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ORIGINAL ARTICLE

Primary cutaneous indolent B-cell lymphomas – a retrospective multicenter analysis and a review of literature

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ABSTRACT

Introduction: Primary cutaneous indolent B-cell lymphomas (PCBCLs) are not well characterized due to their rarity and indolent character.

Methods: We retrospectively reviewed the data from 52 patients with primary cutaneous follicular lymphoma (PCFL) ($n = 26$), marginal zone lymphoma (PCMZL) ($n = 25$) or undefined PCBCL ($n = 1$) treated in 10 hematology centers in 1999–2019.

Results: *Patients characteristics and diagnostic approach:* In almost half of the patients, pruritus or pain were present at diagnosis. The lesions were predominantly located on the head and trunk. The disease was present in a form of solitary infiltration or disseminated lesions with a similar frequency.

Treatment details and outcomes: Surgery, radiotherapy, rituximab alone or combined with chemotherapy were applied as first-line treatment in 33%, 25%, 21% and 21% of patients, with complete response (CR) achieved by 94%, 83%, 50% and 70% of patients, respectively ($p = 0.28$). The median duration of response (DoR) was 65 months (95%CI 35–155).

Survival: After the median follow-up time of 46 months (range: 3–225), the estimated 5-year overall survival (OS) and progression-free survival (PFS) were 93% and 54%, respectively.

Discussion: Clinical presentation was largely consistent with the literature data, however, we observed some differences, including higher predilection to affect upper extremities (25%) and more frequent multifocal appearance in PCFCL (64%) and unifocal in PCMZL (70%).

A high proportion of patients with indolent PCBCL achieved CR after the first-line therapy (77%), regardless of treatment mode. We did not find any impact of clinical features on treatment outcomes.

Conclusions: All treatment modalities resulted in a high overall response rate. Surgery and/or radiotherapy are the optimal therapeutic options for patients with localized disease. The decision to treat systemically should rather be limited to the generalized form of the disease. High response rate, long duration of remission and excellent long-term survival confirm the truly indolent character of PCFCL and PCMZL.

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Introduction

Most cutaneous lymphomas are T-cell-derived neoplasms. Primary cutaneous B-cell lymphomas (PCBCL) present in the skin with no systemic involvement at diagnosis constitute only 20–25% of skin lymphomas, at least 90% of which are primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicular lymphoma (PCFCL) and diffuse large B-cell lymphoma leg-type (DLBCL leg type). The updated WHO-EORTC classification of this group of lymphomas was published in 2018 [1,2].

Indolent PCBCLs affect primarily adults at the age of 40–60 years. The pathogenesis of these lymphomas remains unclear. The potential role of infections in PCMZL etiopathology was suggested by some authors but has not been clearly confirmed yet [3]. The disease localizes preferably within the trunk, head and arms, with lesions that are heterogeneous in their appearance. Large wedge-shaped biopsy and excision biopsy, which enable histological analysis are the golden standard in the diagnostic process. CT scans are the recommended imaging studies although they are not

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Supplemental data for this article can be accessed here.

reliable in cutaneous lesions assessment [4]. Bone marrow examination is not a part of the routine diagnostic workup in indolent PCBCLs. Histologically indolent PCBCLs usually differ from their systemic equivalents [2,5]. Only a small subset of PCMZLs shows diffuse proliferation of B cells while a vast majority of cases show evidence of immunoglobulin class switching. There is some evidence that *t*(14;18) and *Bcl-2* expression may be useful for differentiation between PCFCL and systemic FL [6]. Both TNM and Ann Arbor classification does not appear as useful and reliable in the PCBCLs staging process, as in systemic lymphomas. In 2011 International Extranodal Lymphoma Study Group proposed a new tool for risk stratification, the Cutaneous Lymphoma International Prognostic Index – CLIPI (Supplementary file). However generally, indolent PCBCLs are characterized by a very good prognosis, since 5-year disease-specific survival is as high as 99% for PCMZL and 95% for PCFCL [1].

The localized disease treatment modalities include surgery, radiotherapy and topical treatment. Surgical procedures might be both diagnostic and therapeutic. The efficacy of radiotherapy reported in the literature is high, allowing to achieve complete remission (CR) in more than 95% of patients [2]. In the case of multifocal disease, systemic therapy is recommended but radiotherapy remains an option. Despite a high CR rate after frontline treatment, relapses are relatively frequent, observed in approximately 30–50% of PCFCLs and similarly common in PCMZL patients [2]. Progression to other organs is absolutely rare [7–9].

The goal of our multicenter retrospective study under the auspices of the Polish Lymphoma Research Group (PLRG) was to analyze the data on indolent PCBCLs in order to supplement practical knowledge on clinical presentation, diagnostic approach and treatment outcomes.

Methods

The project was carried under the auspices of PLRG. We retrospectively reviewed the data from 52 patients with PCBCL diagnosis, who were treated in 10 hematology centers in 3 countries (Poland, Spain and France) between 1999 and 2019. Data were collected from the local medical records. The diagnosis of PCBCL was based on the WHO criteria valid at the time of diagnosis for each specific entity. The last patient follow-up was updated in August 2019. The following data was collected in the database: age at diagnosis, gender, diagnostic tools used to determine disease advancement, clinical features e.g., size, number of lesions, genetic characteristics, type of applied treatment, response to treatment (according to Cheson criteria for non-Hodgkin lymphomas), time of progression or relapse and survival status. The quantitative variables (age, number of lesions, the size of lesions in cm) were presented using descriptive statistics, i.e., median, range. According to the Declaration of Helsinki, the protocol was approved by the Research Ethics Board of each participating hospital. Informed consent was obtained from all patients.

In the discussion section, our results were compared to the data published in the literature. For this purpose existing publications were reviewed by two independent reviewers, who used search strategy and selection of studies in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The following databases were searched without restrictions: PubMed and Excerpta Medica database (EMBASE). In addition, reference lists of important studies and reviews were hand searched. The last literature search was performed on 26 July 2020. Similar keywords were used in different databases: primary cutaneous marginal zone lymphoma (PCMZL), primary cutaneous follicular lymphoma (PCFCL). Case reports or studies analyzing a series of patients with PCFCL and PCMZL were selected. Our systematic search obtained 665 citations from databases and journals (529 original research/case report articles and 136 reviews). The agreement between the reviewers in the study selection was excellent (kappa $= 0.97$).

The STROBE cohort reporting guidelines: von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies were used.

Statistics

Patients' characteristics were compared using Kruskal–Wallis test for numerical variables and χ^2 test for categorical variables. Non-parametric test of U Mann–Whitney was employed to compare quantitative variables. Response rates were analyzed using simple descriptive statistics. Differences in response rates among subgroups were analyzed using χ^2 or Fisher's exact test. Survival curves were estimated according to the Kaplan–Meier estimator. Overall survival (OS) was measured from the initiation of therapy until death and progression-free survival (PFS) until documented progression/relapse or death from any cause. The duration of response (DoR) was defined as the time from the achievement of response to progression among responders. The probability of DoR was calculated using the Kaplan–Meier estimator. All *p*-values are two-sided with a type 1 error rate fixed at .05. Statistical analyzes were performed with SPSS version 14.0 (SPSS Inc, Chicago, Illinois) and STATISTICA version 13.3 package (StatSoft Polska, Poland).

Results

Patients characteristics and diagnostic approach

The data of 25 patients with PCFCL, 26 with PCMZL and 1 with undefined indolent PCBCL were included in the analysis. Patients' characteristics and clinical features are listed in Table 1. Considering clinical appearance, microbial inflammation in 3 patients, rheumatic condition in 2 patients and sarcoidosis in 3 patients were reported among potential inflammatory explanations of lesions before the final diagnosis was established. In almost half of the patients, pruritus or pain were present at the time of diagnosis. The lesions were predominantly located on the head and trunk but in

Table 1. Patients' characteristics and clinical manifestations in indolent Primary Cutaneous B-cell Lymphomas.

Characteristic	PCBCL* No (%) or median (range)	PCFCL No (%) or median (range)	PCMZL No (%) or median (range)
Age [years]	61 (21–84)	57 (21–84)	62,5 (29–83)
Histopathology	52	25 (48)	26 (52)
Clinical suspicion			
Solid cancer	9 (17)	5 (20)	4 (15)
Lymphoma	24 (46)	10 (40)	14 (54)
Reactive/inflammation	16 (31)	10 (40)	6 (23)
Missing data	3 (6)	–	2 (8)
Localization			
Trunk	26 (52)	13 (52)	12 (46)
Head	21(40)	13 (52)	8 (31)
Upper extremities	13 (25)	7 (28)	6 (23)
Lower extremities	6 (11)	1 (16)	4 (15)
Number of lesions			
One on one part	3 (6)	1 (4)	2 (7)
Multiple on one part	21 (40)	15 (60)	6 (23)
Solitary	28 (54)	9 (36)	18 (70)
Biggest lesion size [cm]	2 (0.8–10)	2 (0.2–8)	2 (1–10)
Lesion character:			
Nodules	28 (54)	14 (56)	14 (54)
Other	14 (27)	5 (20)	8 (31)
Missing data	10 (19)	6 (24)	4 (15)
Time from first symptoms to diagnosis [months]	6 (1–120)	9 (2–50)	6 (1–120)
Symptoms:			
Pruritus	21 (40)	11 (44)	10 (38)
Pain	3 (6)	2 (8)	1 (4)
No symptoms	29 (56)	14 (56)	15 (58)

PCBCL: primary cutaneous B-cell lymphoma; PCFCL: primary cutaneous follicle center lymphoma; PCMZL: primary marginal zone lymphoma.
*One patient with undefined PCBCL was included in the general group only, thus the numbers may not add up.

approximately 25% of patients (6 with PCMZL and 7 with PCFCL), they were present on upper extremities. Only in 1 out of 25 PCFCL patients lower limbs location was seen. Epidermal involvement, scaling and ulcerations were not reported. The disease was present in a form of solitary infiltration or disseminated lesions with a similar frequency (54% vs. 46%).

Regarding the diagnostic approach, positron emission tomography–computed tomography (PET–CT) was conducted in 17 (36%) patients at diagnosis. Over half of the examined cases were FDG avid, which enabled the assessment of skin involvement in those patients. However, no extracutaneous disease was revealed at diagnosis with PET-CT. Bone marrow biopsy was performed in 33 (63%) patients, revealing bone marrow involvement only in one patient, who was diagnosed with PCMZL and who presented with numerous lesions on the head and extremities. CLIPI was evaluated in 32 patients, with 50% of them classified into high-risk groups (CLIPI $\geq$2). The applied diagnostic procedures are presented in Table 2.

Treatment details and outcomes

Treatment outcome was available in 48 patients. In 2 patients the results were not accessible at the moment of data collection and in addition to that, one patient was lost to follow-up, one patient was not qualified for therapy. The applied treatment modalities regarding 48 patients with available responses to treatment are presented in Table 3. Ten patients (21%) were treated with rituximab administered in monotherapy. Another ten patients (21%) received systemic chemotherapy (CVP: cyclophosphamide, vincristine, prednisone or CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone) combined with rituximab as first-line treatment. In one case rituximab was administered intralesionally. Surgery was performed in 16 patients (33%) (lesions in these patients were 0.8–3 cm in diameter). Radiotherapy alone was applied in 12 patients (25%). All but one patient received a total dose above 12 Gy. Maintenance treatment after first-line treatment was conducted in 3 patients (1 with PCMZL and 2 with PCFCL).

The outcomes of first-line treatment are shown in Table 4. Complete response (CR) was achieved in 83%, 70% and 94% of patients treated with radiotherapy, chemoimmunotherapy and surgical treatment, respectively ($p = 0.28$). The patient with undefined PCBCL was the only non-responder. Regarding the CLIPI, CR was obtained in 94% of patients with low CLIPI scores (0–1) compared to 73% with a high score (2–3) ($p = 0.28$). No association was found between response rate and patient's age, gender, histopathological type, Bcl-2 status, skin lesions location, the form of lesions (nodules vs other) or symptoms (pruritus and pain).

Twenty-one out of 48 analyzed patients experienced relapse or disease progression, including 11 with PCFCL, 9 with PCMZL and 1 with undefined PCBCL. Regarding the therapy mode, lymphoma relapse occurred in 33% of patients (4/12) treated with radiotherapy, 30% (7/20) of those treated with immuno- or chemoimmunotherapy and 43% (7/16) of patients who underwent surgery. At relapse extracutaneous dissemination was revealed in 2 cases, including bone marrow involvement in a patient with PCFCL and lymphadenopathy in a patient with undefined PCBCL. Multifocal lesions were observed in 10 out of 16 cases, including 14

Table 2. Diagnostic tests and procedures used in indolent primary cutaneous B-cell lymphomas.

Diagnostic test/procedure	General No (%)	PCFCLNo (%)	PCMZLNo (%)
Bcl-2 and Bcl-6 status (IHC)			
Data available	38/52 (73)	19/25 (76)	19/26 (73)
Bcl-2 positive	27/38 (71)	10/19 (52)	17/19 (89)
Bcl-6 positive	17/38 (45)	15/19 (79)	2/19 (10)
Bone marrow examination			
Data available	35/52 (67)	16/25 (64)	19/26 (73)
BM Biopsy	33/52 (63)	14/16 (87)	19/19 (100)
BM cytological and cytometric evaluation	2/52 (4)	2/16 (12)	0
BM involvement	1/35 (3)	0 (0)	1/19 (5)
Imaging studies			
Data available	47/52 (90)	23/25 (92)	23/26 (88)
Conventional X-ray and ultrasonography	5/47 (11)	3/23 (13)	2/23 (9)
CT	25/47 (53)	12/23 (52)	13/23 (57)
PET CT – Data available	17/47 (36)	8/23 (35)	9/23 (39)
PET CT positive	9/17 (53)	4/8 (50)	5/9 (56)
LDH			
Data available	33/52 (63)	19/25 (76)	14/26 (54)
Elevated	11/33 (33)	5/19 (26)	5/14 (36)

Bcl-2: B-cell lymphoma 2 gene; Bcl-6: B cell lymphoma 6 gene; BM: bone marrow; CT: computed tomography; IHC: immunochemistry; LDH: lactate dehydrogenase; PCFCL: primary cutaneous follicle center lymphoma; PCMZL: primary marginal zone lymphoma; PET-CT: positron-emission tomography/computed tomography.
The numbers may not add up, since one undefined PCBCL case was only included in the general column.

lesions that reappeared at previously infiltrated sites and another 11 that were found in a different region. Two patients experienced transformation to aggressive lymphoma, one with PCMZL and the other with undefined PCBCL.

The median time of duration of response (DoR) was 65 months (95%CI 35–155). No impact of the type of therapy, clinical features, Bcl-2 status or histopathological type of PCBCL on DoR was found. The estimated 5-year DoR for patients with low/intermediate and high CLIPI was 65% vs. 45%, respectively, however, the difference was not significant ($p = 0.29$).

Survival

The median follow-up time for surviving patients was 46 months (range, 3–225).

The 5-year overall survival (OS) and progression-free survival (PFS) estimates in the whole study group were 93% (95%CI 84–103) and 54% (95%CI 38–70), respectively. Three patients died during the observation period. One of them, a patient with undefined PCBCL, died from disease progression. In two remaining cases, deaths were not associated with lymphoma progression, including one death from stroke and one from pancreatic carcinoma.

No association was found between the patient's age, gender, histopathological type, skin lesions location, the form of lesions (nodules vs other), Bcl-2 status, symptoms, CLIPI, treatment approach and OS. Similarly, no prognostic factors were found for PFS. The estimated 5-year PFS of patients with high CLIPI was 38%, compared to 65% of those with lower CLIPI. However, the difference did not reach statistical significance ($p = 0.198$) (Figure 1).

Discussion

For the purpose of this study, 52 patients have been identified with indolent PCBCLs diagnosed and treated in 10 hematological centers over the past two decades. Both PCFCL and PCMZL were equally frequent according to our data, which is in line with WHO 2018 classification providing similar PCFCL and PCMZL incidence of 12% and 9%, respectively [1]. The median age at diagnosis reported in the literature is 60 years but it varies in a wide range, which is in line with our data [3,8]. According to our findings, the median time from the appearance of skin lesions to the diagnosis was 6 months, whereas Hoefnagel et al. reported 12 months in the study published 15 years ago [9]. That may reflect higher alertness to the skin lesions nowadays, even the slowly progressing ones. The observations also seem to confirm that lesions in indolent PCBCLs may mimic other neoplasms as well as rheumatological or viral diseases. In our retrospective analysis lesions appeared mainly in the form of nodules, which is considered to be a negative prognostic factor in the literature. However, the negative impact of this form of lesions on response rate or DoR was not confirmed. Epidermal involvement, scaling and ulcerations are rare in indolent PCBCLs [9] and were not observed in the study group. Lesions in PCMZL and PCFCL are smaller than those in PCDLBCL – leg type. In our observation, the largest diameter of lesions did not exceed 3 cm. Our data show that apart from typical locations on the head and trunk [10], 25% of patients have lesions on the upper limbs, which differs from the other authors' observations [9].

In contrast to the available literature data, our observations indicate that solitary lesions in PCMZL are much more frequent than multifocal appearance (18 vs. 8 patients) [8,10,11]. In our experience, multifocal lesions are more frequent in patients with PCFCL (16 vs. 9 patients) [9]. Indolent PCBCLs might remain asymptomatic for a long time. More than 50% reported patients did not suffer from any complaints at the diagnosis. If the symptoms appear, they manifest most commonly as local pruritus.

Bone marrow involvement at diagnosis usually excludes primary cutaneous lymphoma [4], however, its presence was described in up to 5–10% of published PCMZL cases [2]. Secondary bone marrow infiltration is considered a negative

Table 3. Overview of publications of retrospective studies with at least 20 patients with primary cutaneous follicular lymphoma or primary marginal zone lymphoma, of which at least some were patients with multifocal disease.

Author, Publication, Year	No. of analyzed patients: PCFCL	No. of analyzed patients: PCMZL	Treatment modality	Complete response rate (%)	Median follow up (months)	Treatment outcomes
Hoefnagel et al. Arch Dermatol 2005 [8]	–	50	Observation, Rth, Chth (no Imt), Surg	Rth: 16 Chth: 20	36	5-y RFS 51% Extracutaneous dissemination 1/50
de la Fouchardiere et al. Ann Pathol 2005 [10]	2	33	Observation, Rth, Chth (no Imt), Surg, Antibiotics	–	24	Extracutaneous dissemination 6/35 (*PCMZL only*) Transformation 2/35 (*PCMZL only*)
Lucioni et al. Cancer Medicine 2016 [9]	96	–	Rth: 47, Chth: 26, Surg: 20,	84 (*majority unifocal*)	47	RR: 43% Extracutaneous dissemination 5/81 MTR: 24 months
Senff et al. JCO 2007 [11]	171	71	Rth: 31 PCMZL, 111 PCFCL, Chth: 5 PCMZL, 35 PCFCL, Surg: 9 PCMZL, 11 PCFCL	81 PCMZL, 98,8 PCFCL	–	RR: 56% PCMZL, 30% PCFCL extracutaneous dissemination: 8,5% PCMZL, 10,5% PCFCL
Hamilton et al. IJRO 2013 [19]	44	59	Rth: 49 PCMZL, 34 PCFCL, Chth: 1 PCMZL, 2 PCFCL, Imt: 1 PCMZL, 2 PCFCL, Surg: 7 PCMZL, 3 PCFCL	95 PCMZL *(88% unifocal)*, 80 PCFCL	46,8	RR: 36% PCMZL, 23% PCFCL
Golling et al. et al. Leukemia Lymphoma 2008 [18]	16	31	Rth: 2 PCMZL, 4 PCFCL, Surg: 11 PCMZL, 16 PCFCL, Antibiotics: 11 PCMZL, 4 PCFCL	Rth: 100 PCMZL, 75 PCFCL, Surg: 91 PCMZL, 67 PCFCL, Antibiotics: 0 PCMZL, 0 PCFCL	63	RR: 71% PCMZL, 43% PCFCL Extracutaneous dissemination – 0
Akhtari et al. Leukemia Lymphoma 2016 [21]	16	21	Rth	Rth: 100	29	RR: 10/42 lesions MTR: 10 months
Senff et al. Blood 2008 *Metaanalysis of 92 articles* [7]	–	–	Rth: 132 PCMZL, 460 PCFCL, Imt: 3 PCMZL, 28 PCFCL, Chth: 33 PCMZL, 104 PCFCL, Surg: 75 PCMZL, 93 PCFCL	Rth: 99 PCMZL, 99 PCFCL, Imt: 67 PCMZL, 75 PCFCL, Chth: 85 PCMZL, 85 PCFCL, Surg: 99 PCMZL, 98 PCFCL	–	RR: Rth: 46% PCMZL, 47% PCFCL, Chth: 57% PCMZL, 14% PCFCL, Surg: 43% PCMZL, 40% PCFCL
Muniesa et al. JAAD 2020 [25]	29	25	Imt (Rituximab x 4)	Imt: 72 PCFCL, 64 PCMZL	90	RR: 41% PCFCL, 48% PCMZL mPFS 62 months

Chth: chemotherapy; CR: complete remission; Imt: immunotherapy; MTR: median time to relapse; PCFCL: primary cutaneous follicle center lymphoma; PCMZL: primary marginal zone lymphoma; PR: partial remission; PFS: progression free survival, RFS: relapse free survival; RR: relapse rate; Rth: radiotherapy; Surg: surgical treatment.

Table 4. First-line therapy results in primary cutaneous indolent B-cell non-Hodgkin lymphoma patients.

	CR No (%)	PR No (%)	RD No (%)
Radiotherapy	10 (83)	2 (17)	0 (0)
Rituximab monotherapy	5 (50)	5 (50)	0 (0)
Rituximab plus chemotherapy	7 (70)	2 (20)	1 (10)
Surgery	15 (94)	1 (6)	0 (0)
Total	37 (77)	10 (21)	1 (2)

CR: complete remission; PR: partial remission; RD: refractory disease.
No: number.

prognostic factor for PCBCL by some authors [7]. Bone marrow examination is not a part of a routine workup in indolent PCBCLs [12]. However, owing to the fact that positive results might advocate systemic therapy, considering bone marrow examination at diagnosis is worth considering in certain cases. Computed tomography (CT) is a standard imaging procedure in PCBCLs to exclude extracutaneous involvement [4] but it does not appear to be useful in skin lesion detection. Kheterpal et al. performed multi-body tomography or PET-CT in patients with PCFCL and PCMZL. The extracutaneous disease was noted in 3.6% and 8.8% of patients with MZL ($n = 306$) and FCL ($n = 21$), with imaging techniques sensitivity 81–90% [13]. CT did not reveal skin lesions present in the physical examination in any of the patients in the study group. Currently, PET-CT is not a method of choice in indolent PCBCLs. Based on our experience, PET-CT can visualize infiltrates undetectable in physical examination, however,

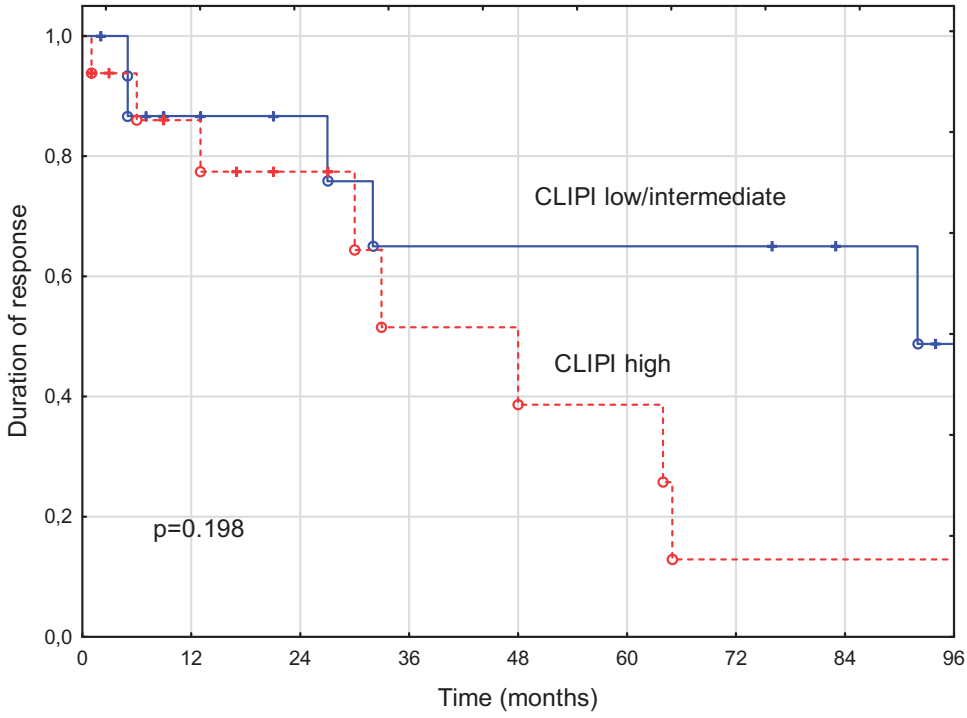

Figure 1. DOR correlation with CLIPI at 5 years for indolent PCBCLs. DOR: duration of response; CLIPI: cutaneous lymphoma international prognostic index; PCBCL: primary cutaneous B cell lymphoma

it should be noted that indolent PCBCL lesions are not avid in a significant proportion of patients.

Focusing on cytogenetics, according to the published data *t*(14;18) resulting in *Bcl-2* translocation is not common in PCFCL in contrast to systemic follicular lymphoma. According to most sources, Bcl-2 expression tested by immunohistochemistry (IHC) in PCFCL is negative or weak [4] but the data analyzed in this research support the observation of Lucioni *et al*., according to whom Bcl-2 is positive in up to 60% of cases in IHC [9]. Depending on the method, *Bcl-2* translocation is present in 8–40% of patients by fluorescence *in situ* hybridization (FISH) and in 13–34% by polymerase chain reaction (PCR) retrospectively [9,14–17].

There is only one prognostic system designed for cutaneous lymphomas, CLIPI (Supplementary file). We evaluated the impact of high CLIPI $\geq$2 on response rate, DOR and PFS. Even though the difference was not statistically significant, numerically the response rate and PFS estimates were worse in patients with a high score (Figure 1). Based on these results, we support CLIPI application in further prospective or observational studies. Leg location in PCFCL is reported as a negative prognostic factor [11], however, only one patient in our study group presented with this location, which obviously did not allow us to assess its prognostic significance. The available literature data regarding Bcl-2 expression significance for treatment outcomes are inconclusive [13]. The results achieved do not indicate any relationship between Bcl-2 expression with response rate, DoR, PFS or OS. No association was found between clinical outcomes and age, gender, location, number or character of lesions, symptoms or CLIPI.

The analysis of treatment efficacy is a real challenge in indolent lymphomas. In numerous cases 'watch and wait' strategy is used successfully for months or even years. Additionally, surgical procedures might be both diagnostic and therapeutic, particularly in localized diseases. The effectiveness of different therapeutic strategies in indolent PCBCLs was compared. Complete excision of the lesion is considered to be generally as efficacious as systemic therapies and results in a similar outcome. In the study group CR rate after excision was very high, reaching 94.5%, while for radiotherapy it was 83.3% and for immunotherapy with or without chemotherapy only 60% (p=ns). Previous data support radiotherapy superiority over surgery [18] and chemotherapy [19], although it is important to remember that not many of them addressed immunotherapy [20] and very few compared immunotherapy to radiotherapy (Table 3). The meta-analysis published by Senff NJ et al. in 2008 allowed to assess response rate in a large group of patients treated with radiotherapy, chemotherapy or surgery [7]. The results of this meta-analysis show the response rate similar to our findings. Nicolay and colleagues also described the high effectiveness (>95%) of radiotherapy and surgical methods in indolent PCBCLs [2]. Regarding radiotherapy, there are conflicting data on de-escalation of radiotherapy dose. Some authors support introducing a lower dose <12 Gy [21,22] but there are some doubts about its efficacy [23]. All but one patient from the cohort were treated with the dose >12 Gy. Surgical treatment and radiotherapy are the methods of choice in indolent primary cutaneous lymphomas, whereas systemic therapy should be considered primarily in disseminated and symptomatic diseases [24].

Recently, Muniesa C et al. performed a retrospective analysis in 54 PCFCL and PCMZL patients treated with rituximab given in monotherapy, as most patients (87%) presented with disseminated disease. The CR rate was 68% and the median PFS reached 62 months [25].

The role of maintenance therapy in PCBCLs has not been established so far, since there are no convincing data on its efficacy in the literature. Only three patients in the study group received maintenance, thus the group is too small to draw any conclusions.

The median duration of response was relatively long in our study, however, 52% of patients relapsed during the follow-up time, with an equal recurrence rate among PCFCL and PCMZL patients. With regard to treatment modality, the relapse rates after radiotherapy, immunotherapy and immunochemotherapy were comparable (33%, 30%, and 43% respectively), in contrast to some previously published data indicating less benefits from surgical excision [7]. The observations seem to suggest that relapses are nearly always confined to the skin, both in PCFCL and PCMZL, which is concordant with most of the previous publications [8,18]. However, some authors showed that a small proportion of patients, about 5-10%, experienced extracutaneous relapses [7]. Golling et al. reported most of the recurrences in primary localizations [18], whereas in our observation relapses appear in distant areas with the same frequency as in previously affected locations. Transformation to more aggressive lymphoma has been uncommon in our cohort, which is in line with the previously published data [10].

The main limitation of our study is associated with its retrospective nature and a limited number of patients. Yet, considering the rarity of these types of lymphoma, our patient collective with 52 cases does add additional value to the current state of knowledge.

Conclusions

Clinical manifestation of PCFCL and PCMZL in our analysis is generally similar to the literature data, however, with differences in higher predilection to affect upper extremities, more frequent multifocal appearance in PCFCL and unifocal in PCMZL. A relatively high rate of Bcl-2 expression in PCFCL has been observed. All treatment modalities resulted in a high overall response rate, with a very good effect of surgical excision that may serve as both, a diagnostic and a therapeutic tool. The data collected in this study also suggest very good results of radiotherapy. Given the comparable effects of described therapies and the relapsing nature of the disease, it must be emphasized that surgery and/or radiotherapy are the optimal therapeutic options for patients with localized disease. The decision to treat systemically should rather be limited to the generalized form of the disease. In summary, high response rate, long duration of remission and excellent long-term survival confirm the indolent character of PCFCL and PCMZL.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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