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

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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 (PCDLBLCL, 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 empiric 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 (oral, 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 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

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

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.
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,
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: gemcitabine (10 pts), liposomal doxorubicin (11 pts), cytarabine (4 pts), pralatrexate (1 pt), hexametone (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 – autologous 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 synchronous and breast cancer was treated with AC chemotherapy with subsequent breast-conserving surgery followed by radiotherapy.

5 patients 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 present 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 immunotherapy 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

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


80
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, mecrolhethamine, 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 IIIB–III), fludarabine (ORR = 55% in stage IA–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 (IIIB–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 everyday 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 lymphoproliferative 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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