Diagnostic and prognostic markers of cutaneous lymphomas

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CHAPTER

HIGH INCIDENCE AND CLINICAL SIGNIFICANCE OF *MYC* REARRANGEMENTS IN PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, LEG TYPE

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ABSTRACT

Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) and primary cutaneous follicle center lymphoma (PCFCL) are cutaneous B-cell lymphomas (CBCL) with different clinical characteristics and behavior. PCDLBCL-LT is the most aggressive CBCL with a relatively poor prognosis. In nodal diffuse large B-cell lymphoma (DLBCL), rearrangements of the *MYC* gene, especially in combination with a second hit in *BCL2* and/or *BCL6*, and double protein expression of MYC and BCL2 (DE) are adverse prognostic factors. As the clinical significance of these factors in CBCL is largely unknown, we studied the frequency and prognostic value of *MYC* rearrangements and DE in a cohort of 44 patients with PCDLBCL-LT and 17 patients with PCFCL. Compared with nodal DLBCL (9 to 14%), the PCDLBCL-LT patients had a high incidence of *MYC* rearrangements (32%), but only 2 (4%) patients had a second hit, both with *BCL6*. PCDLBCL-LT patients with a *MYC* rearrangement showed an inferior disease-specific survival (Log-rank, p=0.036) and disease-free survival (Log-rank, p=0.028), but no significant adverse effect on overall survival (Log-rank, p=0.157) at 5 years compared with patients without a *MYC* rearrangement. DE, present in 65% of the PCDLBCL-LT patients, was not associated with reduced survival. In the PCFCL group, *MYC* rearrangements and DE were not detected. In conclusion, this study identifies a high incidence of *MYC* rearrangements in PCDLBCL-LT compared with nodal DLBCL and further shows that a *MYC* rearrangement is an inferior prognostic marker in these patients. Therefore, our data suggest that it is useful to perform *MYC*-FISH in all newly diagnosed PCDLBCL-LT patients.

INTRODUCTION

Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) and primary cutaneous follicle center lymphoma (PCFCL) are both cutaneous B-cell lymphomas (CBCL) with a large cell morphology. Whereas PCFCL patients have an excellent prognosis with a 5-year disease-specific survival (DSS) of over 95%, PCDLBCL-LT is a more aggressive type of CBCL with a 5-year DSS of ~55%.[1] So far, the only adverse prognostic factors that have been identified are presentation with multiple skin lesions, loss of 9p.21 (*CDKN2A/B*), and hotspot mutations in *MYD88* L265P.[2-4]

In 9 to 14% of nodal diffuse large B-cell lymphomas (DLBCLs), rearrangements of the *MYC* gene are present, which is associated with a poor prognosis.[5-8] In over half of the cases, MYC rearrangements occur in combination with a second hit in the *BCL2* and/or *BCL6* genes and these patients demonstrate an even worse outcome with a median overall survival (OS) reported between 0.2 and 1.5 years.[5,8-12] In the 2017 revision of the World Health Organization (WHO) classification, these so called "double hit lymphomas" (or "triple hit lymphomas") are classified as a separate disease entity with a very aggressive behavior.[13] In addition, 19 to 34% of the DLBCL patients have double protein expression of MYC and BCL2 (DE), but lack genetic rearrangements in these genes, demonstrating an intermediate survival between DLBCL with single or no expression of MYC and BCL2, and DLBCL with double or triple hits.[14-16] Regarding the cell-of-origin, single *MYC* rearrangements and double hits with *BCL6* show a rather equal distribution between the germinal center B-cell (GCB) and the activated B-cell (ABC) subtypes, whereas double hits with *BCL2* and triple hits are characteristic for GCB-DLBCL and do not seem to occur in ABC-DLBCL.[17] In addition, DE is more common in the ABC subtype.[16]

Gene-expression profiling of CBCL showed that PCDLBCL-LT is similar to the ABC-subtype and PCFCL to the GCB-subtype of nodal DLBCL.[18] Correspondingly, the vast majority of PCDLBCL-LT patients expresses MUM1 and BCL2, approximately two-thirds is positive for BCL6, while CD10 expression is usually lacking.[19,20] Molecular studies identified highly recurrent mutations in genes that are

predominantly involved in the NF-κB-signalling pathway, such as *MYD88, PIM1,* and *CD79B*.[21-23] The presence of *MYC* rearrangements and MYC protein expression has only been studied in a small number of patients with CBCL with very diverse results and the relation between *MYC* rearrangements and survival is unknown.[22,24-26]

Considering the small number of studied CBCL patients and the clinical relevance in nodal DLBCL, the purpose of this study was to evaluate the frequency and prognostic significance of *MYC* rearrangements, either alone or in combination with *BCL2* and/or *BCL6* rearrangements, and of DE in a relatively large cohort of PCDLBCL-LT and PCFCL patients.

MATERIALS AND METHODS

All patients with PCDLBCL-LT, consecutively diagnosed in the Leiden University Medical Center (LUMC), Leiden, The Netherlands between 2000 and 2017, were selected from the Cutaneous Lymphoma database (n=47). In addition, a random selection of patients with PCFCL, diagnosed in the same period, were included (n=20). In all cases, diagnoses was confirmed by a panel of dermatologists and pathologist during one of the regular meetings of the Dutch Cutaneous Lymphoma Group, according to the criteria of the WHO and the European Organization for Research and Treatment of Cancer (WHO-EORTC) classification.[1] In all patients, the presence of extracutaneous disease at time of diagnosis was excluded by standard staging procedures, consisting of a combination of physical examination, complete blood count and chemistry, chest radiography, computerized tomography of thorax and abdomen, and bone marrow cytology and/or histology. Clinical presentation and follow-up data were collected from the registry of the Dutch Cutaneous Lymphoma Group and/or from the medical records. Patients were excluded in case of insufficient tissue samples for molecular analysis (n=3 for PCDLBCL-LT; n=3 for PCFCL). The study was performed in accordance with the Code Proper Secondary Use of Human Tissue established by the Dutch Federation of Medical Sciences, as approved by the medical ethics committee of the LUMC (B16.048).

Immunohistochemistry

The pretreatment formalin-fixed and paraffin-embedded skin biopsies from the included patients were collected from the archives of the Department of Pathology of the LUMC. Sections of 3 µm were immunostained with antibodies against MYC (clone Y69, diluted 1:100; ABCAM), BCL2 (clone 124, diluted 1:80; Dako, Glostrup, Denmark), BCL6 (clone PG-B6p, diluted 1:100; Invitrogen), CD20 (clone L26, diluted 1:800; Dako) and/or CD79A (clone JCD117, diluted 1:100; Dako), CD10 (clone 56C6, diluted 1:20; Dako), MUM1 (clone MUM1p, diluted 1:100; Dako), and IgM (polyclonal, diluted 1:500; Dako) using the Dako Autostainer Link 48 according to standard staining procedures. Immunohistochemical expression by the tumor cells was estimated by the authors A.M.R.S., P.M.J., and R.W., until consensus was reached. MYC expression was scored with the standard cutoff value of 40%.[27] The other immunohistochemical markers were scored with a cutoff value of 30% for CD10, BCL6, and MUM1, and 50% for BCL2 and IgM. DE was defined as combined expression of MYC and BCL2.

Fluorescence *in situ* hybridization

Fluorescence *in situ* hybridization (FISH) was performed with Vysis Dual Color Break Apart Rearrangement Probes from Abbott using the Dako Histology FISH Accessory Kit, according to standard procedures. All cases were manually scored by A.M.R.S. and J.K.K. and considered rearranged with a split of the signals in ≥10% of the tumor cells. In case of a *MYC* rearrangement, additional FISH for *BCL2* and *BCL6* was performed with Vysis Dual Color Break Apart Rearrangement Probes from Abbott and the Dako Histology FISH Accessory Kit, according to the same procedures. In the PCFCL group, FISH for *BCL2 w*as also performed on cases with BCL2 expression.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 23. Survival was defined as the date of diagnosis until the date of death by any cause (OS) or the date of death from lymphoma (DSS). Disease-free survival (DFS) was calculated from the date of diagnosis until the time of relapse or progression of disease or death from lymphoma. Patients without an event at the last date of follow-up were censored. For the DSS and DFS, patients who died from an unrelated cause were

also censored. Comparison between the subgroups based on *MYC* rearrangements and DE occurred with the Mann-Whitney U test for continuous data and the χ^2 test for categorical data. Survival curves were plotted using the Kaplan-Meier method and compared with the Log-rank test. Corresponding hazard ratios (HRs) and their 95% confidence intervals (95% CIs) were calculated in a Cox proportional-hazards model. A p-value of <0.05 was considered statistically significant.

RESULTS

In total, 44 patients with PCDLBCL-LT were included: 25 (57%) females and 19 (43%) males. The patient characteristics and an overview of the results are presented in Figure 1 and Table 1. The median age at diagnosis was 78 (range, 49 to 92) years. At presentation, disease was located on the legs in 35 (80%) patients and in sites other than the legs in 9 (20%) patients. Extent of disease was solitary in 11 (25%) patients, localized (multiple lesions in 1 body region) in 28 (64%) patients, and generalized (multiple lesions in more than 1 body region) in 5 (11%) patients. Histologically, the skin lesions showed a diffuse infiltrate of centroblasts and immunoblasts throughout the entire dermis, in some cases extending into the subcutaneous tissue (Figure 2). These B cells showed uniform and strong expression of BCL2 in 42 (95%) cases, MUM1 in 36 (84%) cases and IgM in 42 (95%) cases, while expression of CD10 was seen in 7 (16%) patients, with a very weak expression in 3 of them. In addition, BCL6 was positive in 27 (61%) patients.

The PCFCL group consisted of 17 patients, including 5 (29%) females and 12 (71%) males. Patients were diagnosed at a median age of 58 (range, 46 to 69) years. In all patients, lesions were located on the head or trunk, and in 1 patient also a leg was involved. Histologically, the growth pattern was follicular in 2 (12%) cases, follicular/diffuse in 4 (24%) cases, and diffuse in 11 (65%) cases. The tumor cells were positive for BCL6 in all cases and for CD10 in 14 (82%) cases, while none of the cases expressed MUM1. BCL2 was expressed in 2 (12%) cases, of which 1 case harboured a *BCL2* rearrangement. Two other cases (12%) had membranous staining of IgM.

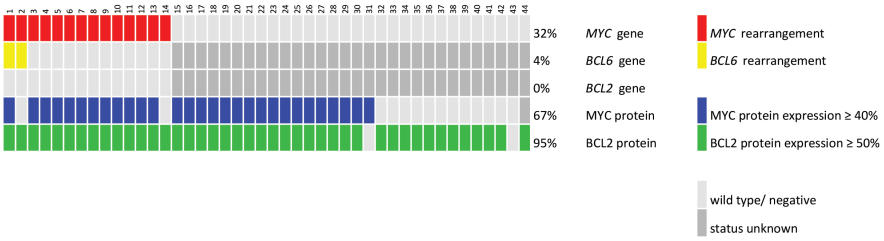

Figure 1. Overview of results of fluorescence *in situ* hybridization for *MYC*, *BCL2,* and *BCL6* and immunohistochemistry for MYC and BCL2 in 44 patients with primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT). The oncoprint shows a *MYC* rearrangement in 32% with a double hit in *BCL6* in 4%, and no double hits in *BCL2*. Protein expression of MYC was present in 67% and BCL2 in 95% with double expression of MYC and BCL2 in 65% of the patients.

Follow-up and survival

The PCDLBCL-LT patients were initially treated with immune-polychemotherapy (CHOP with rituximab) in 16 (36%) cases, chemotherapy (CHOP) in 6 (14%) cases, local radiotherapy in 20 (45%) cases, and surgery alone in 1 (2%) case. In 1 (2%) other patient, no treatment was given due to spontaneous remission of a solitary lesion. After initial therapy, 41 (93%) patients reached complete remission. Twenty-three (52%) patients developed cutaneous relapses during follow-up and 15 (34%) patients had relapses at extracutaneous sites. The median disease-free period was 12 (range, 0 to 105) months. After a median duration of follow-up of 41 (range, 4 to 125) months, 15 (34%) patients were still alive with or without ongoing disease, 20 (45%) patients died from lymphoma and 9 (20%) patients died from an unrelated cause. In our cohort of PCDLBCL-LT patients, OS was 46%, DSS was 52%, and DFS was 39% at 5 years.

In the PCFCL group, all cases reached complete remission after initial treatment. The median duration of follow-up was 63 (range, 4 to 224) months during which skin relapses occurred in 11 (65%) patients, and 2 (12%) patients had extracutaneous dissemination (in both cases to lymph nodes). After follow-up, all patients were still alive with or without ongoing disease, resulting in a 5-year OS and DSS of 100%.

Table 1. Patient characteristics and overview of results of 44 patients with primary cutaneous diffuse large B-cell lymphoma, leg type

		MYC status			Double expression[a]		
Characteristic	**Total (n=44)**	**rearranged (n=14)**	**wild type (n=30)**	**p-value***	**present (n=28)**	**absent (n=15)**	**p-value****
Sex, n (%)				.976			.811
female	25 (57)	8 (57)	17 (57)		16 (57)	8 (53)	
male	19 (43)	6 (43)	13 (43)		12 (43)	7 (47)	
Age at diagnosis in years, median (range)	78 (49-92)	78.5 (49-86)	78 (53-92)	.622	78.5 (49-90)	78 (53-92)	.540
Disease localisation, n (%)				.362			.499
legs	35 (80)	10 (71)	25 (83)		23 (82)	11 (73)	
other sites	9 (20)	4 (29)	5 (17)		5 (18)	4 (27)	
Extent of disease, n (%)	11 (25)	2 (14)	9 (30)	.250	6 (21)	4 (27)	.220
solitary							
localized	28 (64)	9 (64)	19 (63)		17 (61)	11 (73)	
generalized	5 (11)	3 (21)	2 (7)		5 (18)	-	
Initial therapy, n (%)				**.035**			.128
local therapy[a]	21 (48)	3 (21)	18 (60)		11 (39)	9 (60)	
immunochemotherapy (R-CHOP)[b]	16 (36)	6 (43)	10 (33)		10 (36)	6 (40)	
chemotherapy (CHOP)[b]	6 (14)	4 (29)	2 (7)		6 (21)	-	
no treatment[c]	1 (2)	1 (7)	-		1 (4)	-	
Status at last follow-up, n (%)				.157			.283
alive w/o disease	11 (25)	1 (7)	10 (33)		5 (18)	6 (40)	
alive w/ disease	4 (9)	2 (14)	2 (7)		3 (11)	1 (7)	
died of lymphoma	20 (45)	9 (64)	11 (37)		13 (46)	7 (47)	
died unrelated	9 (20)	2 (14)	7 (23)		7 (25)	1 (7)	

Table 1. Patient characteristics and overview of results of 44 patients with primary cutaneous diffuse large B-cell lymphoma, leg type (continued)

		MYC status			Double expression[a]		
Characteristic	**Total (n=44)**	**rearranged (n=14)**	**wild type (n=30)**	**p-value***	**present (n=28)**	**absent (n=15)**	**p-value****
5-year overall survival, %	46	30	52	.157	44	53	.718
5-year disease-specific survival, %	52	30	62	**.036**	51	53	.898
5-year disease-free survival, %	44	25	53	**.028**	41	49	.815
Immunophenotype, n (%)							
MYC[d]	29 (67)	12 (86)	17 (59)	.086	28 (100)	1(7)	NA
CD10	7 (16)	0 (0)	7 (23)	**.049**	6 (21)	1 (7)	.211
BCL6	27 (61)	6 (43)	21 (70)	.085	18 (64)	8 (53)	.484
MUM1[d]	36 (84)	10 (71)	26 (90)	.129	23 (82)	13 (87)	.702
BCL2	42 (95)	14 (100)	28 (93)	.323	28 (100)	13 (87)	NA
IgM	42 (95)	13 (93)	29 (97)	.572	27 (96)	14 (93)	.646
MYC status, n (%)				NA			**.049**
rearrangement	14 (32)	NA	NA		12 (43)	2 (13)	
wild type	30 (68)				16 (57)	13 (87)	
Double hit[e]	2 (4)	2 (14)	NA	NA	1 (4)	1 (7)	.646

Abbreviations: R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; NA, not applicable.

[a]*Local therapy consisted of radiotherapy alone in 19 patients, radiotherapy with surgical excision in 1 patient, and surgical excision alone in 1 patient.*

[b] *(Immuno)chemotherapy was combined with radiotherapy in 9 patients.*

[c] *No treatment was given due to spontaneous remission of the solitary lesion.*

[d]*Data is missing in 1 case.*

[e]*Double hits occurred only in combination with BCL6, not with BCL2.*

**Comparison between MYC-rearranged and MYC-wild type patients.*

***Comparison between patients with and without double expression of MYC and BCL2.*

MYC rearrangements and double expression

In total, 14 (32%) PCDLBCL-LT cases showed a rearrangement of the *MYC* gene, with a double hit of *BCL6* in 2 of them. No double hits with *BCL2* were present. Interestingly, CD10 expression was only observed in patients with wild type *MYC*. DE was seen in 28 of 43 (65%) patients, including 12 of the 14 (86%) cases with a *MYC* rearrangement and 1 of the 2 cases with a double hit (Figure 2). The other double hit case was negative for MYC with expression in ~30% of the tumor cells. Since 95% of the patients with PCDLBCL-LT expressed BCL2, the frequency of DE (65%) was similar to expression of MYC alone (29/43; 67%).

All 17 cases of PCFCL were *MYC*-wild type and none of the cases expressed MYC. In 15 (88%) cases, MYC was only expressed by <10% of the tumor cells, and the remaining 2 cases expressed MYC in ~20% of the tumor cells. For comparison, in the PCDLBCL-LT group, only 4 of 43 (9%) cases expressed MYC in <10% of the tumor cells. As MYC was always negative, none of the PCFCL cases were double expressors.

Prognostic factors

In PCDLBCL-LT patients, the presence of a *MYC* rearrangement was associated with a statistically significantly reduced 5-year DSS (Log-rank, p=0.036; HR, 2.67, 95% CI, 1.03-6.96; Figure 3A) and DFS (Log-rank, p=0.028; HR, 2.47, 95% CI, 1.05-5.78; Figure 3B), but not with a reduced OS (Log-rank, p=0.157; HR, 1.87, 95% CI, 0.77-4.53; Figure 3C). Expression of MYC alone or in combination with BCL2 (DE) had no adverse effect on survival (data not shown).

The 2 PCDLBCL-LT patients with a double hit had a favorable disease course. Notably, in both patients, disease was located on the abdomen and not on the legs (Figure 2). Both patients were initially treated with radiotherapy with complete regression of the lesions. One patient remained disease-free and died after 86 months from an unrelated cause, while the other double hit patient developed positive inguinal lymph nodes after 17 months of follow-up, but reached complete remission after R-CHOP treatment (8x) with a total follow-up duration of 40 months.

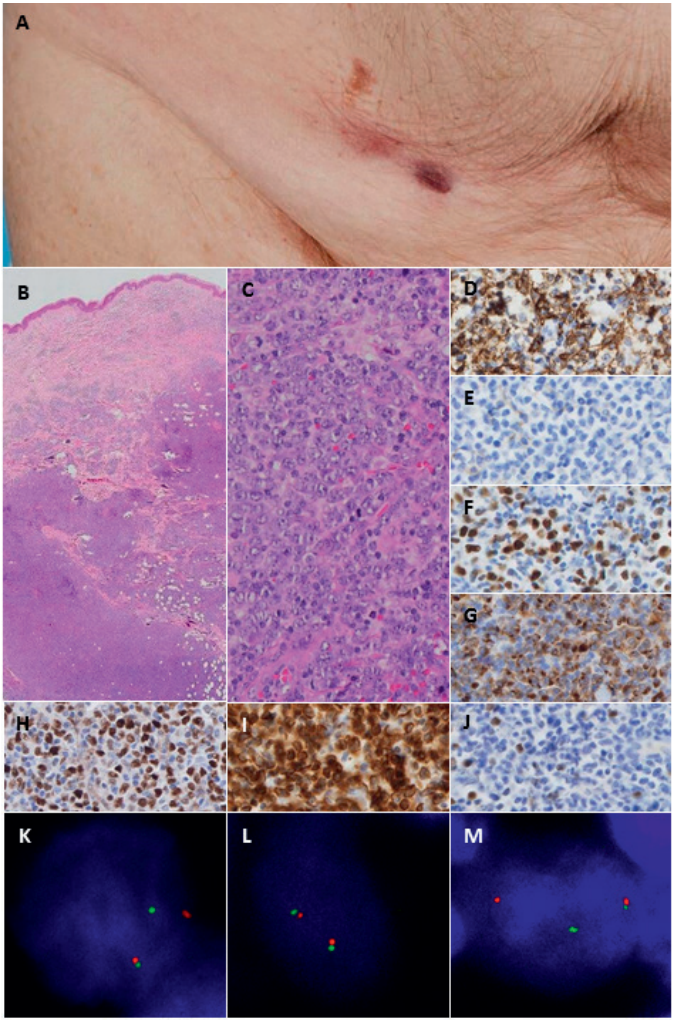

Figure 2. Clinical presentation, histology, and fluorescence *in situ* hybridization (FISH) of a patient with primary cutaneous diffuse large B-cell lymphoma, leg type with a double hit in *MYC* and *BCL6*. The skin of the lower abdomen shows brown to reddish, infiltrated tumors (A). The hematoxylin-eosin stainings (B, magnification x 10; C, magnification x 400) show diffuse dermal sheets of large, blastic cells with prominent nucleoli and mitotic figures with infiltration of the subcutaneous tissue and sparing of the epidermis. The tumor cells are positive for CD20 (D), MUM1 (F), IgM (G), BCL2 (I), and MYC (H), but negative for CD10 (E) and BCL6 (J). FISH shows rearrangements of *MYC* (K) and *BCL6* (M), and no rearrangement of *BCL2* (L).

DISCUSSION

In the present study, we investigated the frequency and prognostic significance of *MYC* rearrangements with or without a double hit in *BCL2* and/or *BCL6* and of DE in 44 patients with PCDLBCL-LT and 17 patients with PCFCL. A subset of 32% of the PCDLBCL-LT patients had a rearrangement of the *MYC* gene, with a double hit in *BCL6* in 2 of these patients, while all PCFCL cases were *MYC*-wild type. The percentage of *MYC* rearrangements in PCDLBCL-LT falls within the wide range of the previously reported studies with small patient numbers (0% to 43%).[22,24-26] Our frequency, however, is higher than reported in nodal DLBCL (9 to 14%) [5-8] and other extranodal DLBCL, such as DLBCL of the central nervous system (PCNSL) (up to 9%).[28-30] Similar to nodal DLBCL in which *MYC* rearrangements are associated with a poor outcome, PCDLBCL-LT patients with a *MYC* rearrangement had a statistically significant inferior 5-year DSS and DFS compared with PCDLBCL-LT patients without a *MYC* rearrangement (Figure 3).

To the best of our knowledge, this is the first study that reports the presence of double hits in PCDLBCL-LT patients. In our cohort, 2 of the *MYC*-rearranged patients had a double hit in *BCL6*. A double hit with *BCL6* instead of *BCL2* is in line with expectations, as in nodal DLBCL with an ABC phenotype, double hits with *BCL2* do not occur.[17] Similarly, in PCNSL, that also has an ABC phenotype, a case report describes a patient with a double hit involving *BCL6* and not *BCL2*.[29] Notably, the disease course of the PCDLBCL-LT patients with a double hit seemed favorable compared with the patients with a single or no *MYC* rearrangement, but the number is too small to draw any conclusions. This finding, however, is in line with the presence of a double hit in *BCL6* instead of *BCL2*, as in nodal DLBCL, the association with poor outcome especially accounts for cases with a double hit in *BCL2* or triple hits, and less for patients with a double hit in *BCL6*.[6,7,31] Despite the GCB-phenotype of PCFCL, no *MYC* hits, nor double hits, were present in our group of PCFCL patients. This is in line with previous studies[24,32], except for a study that reported DE in 6 of 21 (29%) cases of PCFCL including 1 case with a double hit in *MYC* and *BCL6*.[26]

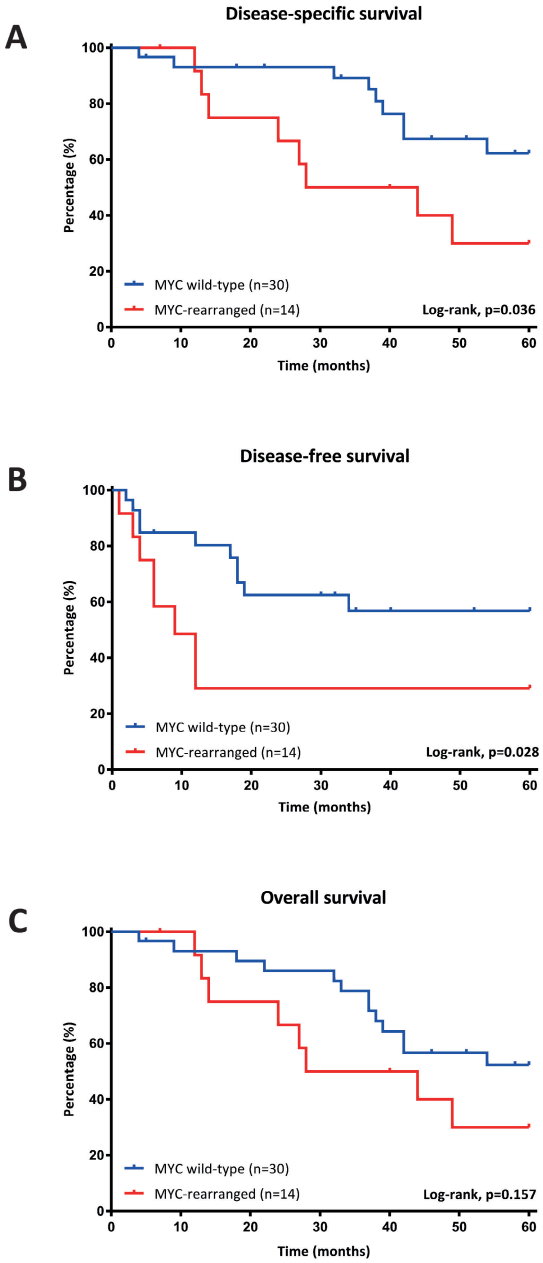

Figure 3. Survival analysis for *MYC* status in 44 patients with primary cutaneous diffuse large B-cell lymphoma, leg type. Kaplan-Meier survival curves show a statistically significant adverse effect on (A) disease-specific survival (Log-rank, p=0.036; HR, 2.67; 95% CI, 1.03-6.96), and (B) disease-free survival (Log-rank, p=0.028; HR, 2.47; 95% CI, 1.05-5.78), but not on (C) overall survival of the patients (Log-rank, p=0.157; HR, 1.87; 95% CI, 0.77-4.53) at 5 years. Survival was defined as the date of diagnosis until the date of death by any cause (overall survival) or the date of death from lymphoma (disease-specific survival). Disease-free survival was calculated from the date of diagnosis until the time of progression or relapse of disease or death from lymphoma. Patients without an event at the last date of follow-up were censored.

In contrast to reported studies in nodal DLBCL [14,15] and PCNSL [33-35], DE was not associated with an inferior survival in our cohort of patients with PCDLBCL-LT. Few studies with a limited number of patients evaluated the prognostic significance of DE in CBCL, showing an inferior survival for the group as a whole -as can be expected by the differences in immune profile and prognosis of PCDLBCL-LT and PCFCL patients-, but with contradicting results for only the PCDLBCL-LT patients.[26,32] As almost all cases of PCDLBCL-LT expressed BCL2, which is a known characteristic of this disease[19,20], the percentage of DE (65%) was similar to MYC expression alone (67%). The percentage of DE in our cohort of PCDLBCL-LT patients corresponds with previously reported percentages of 55 to 83%.[22,26,32] In addition, MYC protein expression was not suitable for the prediction of a *MYC* rearrangement with especially a low positive predictive value of 41%. Some studies suggest that a cutoff value of 70% for MYC has the highest predictive value[36], however, this was not confirmed in our study with only a slight improvement of the positive predictive value to 56%.

On the basis of our results with high frequency and prognostic significance of *MYC* rearrangements in PCDLBCL-LT but not PCFCL, we suggest that it may be useful to perform *MYC*-FISH in all newly diagnosed PCDLBCL-LT patients, as is currently also standard practice in newly diagnosed nodal DLBCL patients.[27] Because of the rarity of double hits in our cohort, the absence in previous studies[22,24], and the combination of a double hit with *BCL6* instead of *BCL2*, additional FISH for *BCL2* and *BCL6* in case of a *MYC* rearrangement seems to have no clinical relevance in patients with PCDLBCL-LT. Immunostaining for MYC protein may be used as an adjunctive marker to differentiate between PCDLBCL-LT and PCFCL with a diffuse large cell morphology in equivocal cases, but is not useful as a prognostic marker, nor as a predictive marker for a *MYC* rearrangement.

This study demonstrates that *MYC*-rearranged PCDLBCL-LT patients may need more intensive disease monitoring during follow-up due to the higher risk for disease-progression and death from lymphoma. Also, the presence of a *MYC* rearrangement in PCDLBCL-LT patients may be interesting with regard to therapeutic strategies, such as intensifying chemotherapeutic regimens using dose-adjusted

EPOCH-R instead of R-CHOP, which is also well tolerated in patients older than 60 years.[37] Moreover, in the future possible new therapies may be developed targeting the *MYC* pathway with restoration of the immune response.[38]

In conclusion, this study identifies a high incidence of *MYC* rearrangements in PCDLBCL-LT but not in PCFCL and suggests that PCDLBCL-LT patients with a *MYC* rearrangement have a higher risk for disease-progression and death from lymphoma. Therefore, it may be useful to perform *MYC*-FISH in all newly diagnosed PCDLBCL-LT patients.

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