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Footnotes

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Data of the DESTINY trial are already presented in Clark et al.[10,11]

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TO THE EDITOR:

Outcomes of rare patients with a primary cutaneous CD30$^+$ lymphoproliferative disorder developing extracutaneous disease

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Primary cutaneous CD30-positive lymphoproliferative disorders (pcCD30$^+$LPDs) account for ~30% of all cutaneous T-cell lymphomas.[1,2] This group forms a spectrum, with primary cutaneous anaplastic large cell lymphoma (C-ALCL) on one end, lymphomatoid papulosis (LyP) on the other, and borderline cases in-between.[3] Patients with C-ALCL mainly present with solitary or localized tumors. Patients with LyP present with a waxing and waning eruption of multiple papular and/or nodular skin lesions

that exhibit spontaneous remission of individual lesions. Both conditions have an excellent prognosis with a 10-year disease-specific survival rate of 90% for C-ALCL and almost 100% for LyP.[1,3] However, a small proportion of patients will develop extracutaneous localizations during follow-up and may require systemic treatment.[1,3-5] At present, only limited data are available regarding therapeutic management of patients developing extracutaneous disease, and the optimal therapy is unknown.[3,6-9] Former treatment guidelines suggest anthracycline-based chemotherapy (eg, cyclophosphamide, doxorubicin, vincristine, and prednisone).[1,3,8,10,11] Unfortunately, information on the efficacy of these therapies is scarce but is essential as a benchmark for novel targeted therapies and for the development of therapeutic algorithms. This knowledge gap motivated us to evaluate current treatment results and prognosis of rare patients with pcCD30$^+$LPDs who developed extracutaneous disease.

We identified 313 patients with C-ALCL and 472 patients with LyP who were included in the Dutch registry of cutaneous lymphomas between October 1985 and December 2017. Diagnosis was made by an expert panel of dermatologists and pathologists from the Dutch Cutaneous Lymphoma Group following the clinicopathologic criteria of the World Health Organization–European Organisation for Research and Treatment of Cancer classification.[1] In all patients with C-ALCL, extracutaneous disease was excluded at time of diagnosis by using routine staging procedures (complete blood count, biochemical analysis, and computed tomography scan of chest, abdomen, and neck). Extracutaneous dissemination was defined as the development of histologically proven systemic localizations after diagnosis of C-ALCL/LyP.[12] Follow-up data showed that 51 (6.5%) of 785 patients, including 38 of 313 with C-ALCL (12%) and 13 of 472 with LyP (3%), had developed extracutaneous manifestations. Patients with an anaplastic lymphoma kinase (ALK)-positive C-ALCL (n = 1), insufficient follow-up data (n = 4), or underlying immunodeficiency (n = 3) were excluded. The final study group of 43 patients included 30 patients with C-ALCL and 13 patients with LyP. Response rates (complete response [CR], partial response [PR], or no response or progressive disease [NR]) and patient outcomes were assessed following the European Organisation for Research and Treatment of Cancer, International Society for Cutaneous Lymphomas, and United States Cutaneous Lymphoma Consortium consensus guidelines for primary cutaneous CD30$^+$LPDs.[11] For the purpose of the study, no distinction was made between different anthracycline-based chemotherapies. This retrospective study was evaluated by the Ethics Committee of the Leiden University Medical Centre and provided with a waiver of consent (G18.118).

The Kaplan-Meier method was used to estimate (5-year) progression-free survival (PFS/PFS5) and overall survival (OS/OS5). Probabilities of (5-year) relapse and (5-year) disease-specific death (DSD/DSD5) over time were calculated with cumulative incidences, taking into account competing risks (any death for relapse, death from unrelated causes for DSD). Comparison between groups was performed by using the log-rank test. A P value $<.05$ was considered significant. All statistical analyses were performed by using SPSS version 23 (IBM SPSS Statistics, IBM Corporation).

The 43 patients with pcCD30$^+$LPD who developed histologically proven extracutaneous disease during follow-up included 31 male patients and 12 female patients (male-to-female ratio, ~3:1); the median age at initial diagnosis was 53 years (range, 26-79 years). Clinical characteristics and treatment responses before extracutaneous dissemination are presented in Table 1. After a median follow-up period of 35 months (range, 5-264 months), 32 patients developed nodal involvement, and 11 patients developed both nodal and visceral involvement. Most patients (34 of 43; 79%) were treated with anthracycline-based chemotherapies (detailed information is provided in supplemental Table 1, available on the *Blood* Web site). Four patients (9%) were treated with radiotherapy (RT), and five patients (12%) received no further therapy, due to patient refusal (n = 1), spontaneous regression (n = 1), or death before treatment initiation (n = 3). Overall, a CR of the extracutaneous manifestations was achieved in 26 (61%) of 43 patients and a PR in 4 (9%) of 43; 13 (30%) of 43 patients had NR. For patients treated with anthracycline-based chemotherapy specifically (n = 34; 79%), a CR was reached in 21 (62%) of 34 patients, a PR in 4 (12%) of 34, and NR in 9 (26%) of 34. All 4 patients treated with RT reached a CR (Table 2).

After treatment of extracutaneous disease, a 48% five-year cumulative incidence of relapse was reported in 26 patients with a CR, including skin-limited (n = 10), systemic (n = 3), and combined cutaneous and systemic (n = 3) relapses. Systemic relapses were only observed in patients with C-ALCL, whereas patients with LyP developed only skin-limited relapses (Table 2). Median time to relapse after extracutaneous treatment was 41 months (range, 4-101 months), and PFS5 was 39%. After a median follow-up period of 81 months (range, 12-360 months), 17 of 43 patients were alive without disease, 4 of 43 were alive with disease, and 19 of 43 had died of lymphoma and 3 of 43 patients had died of other causes. Five-year DSD and OS5 were both 47%.

Interestingly, 13 patients with solitary or localized skin lesions and only involvement of locoregional lymph nodes (T1-2;N1;M0) showed superior response rates and prognosis (11 of 13 [85%] CR, 62% PFS5, and 62% OS5) compared with 30 other patients developing more extensive extracutaneous disease (15 of 30 [50%] CR, 29% PFS5, and 41% OS5) (supplemental Table 2; supplemental Figure 1). In particular, patients with M1 disease showed poor outcomes (2 of 11 [18%] CR, 18% PFS5, and 18% OS5).

Although extracutaneous manifestations occurred more frequently in C-ALCL compared with LyP (11% vs 3%, respectively), the disease course after extracutaneous localizations was comparable (PFS, P = .42; DSD, P = .77; OS, P = .48).

The observed response rates and prognosis of patients with pcCD30$^+$LPDs after extracutaneous development are very similar to results reported in ALK-negative systemic ALCL, showing that a similar treatment approach is indicated.[13-15] Anthracycline-based therapies have been used as first-line treatment in systemic ALCL and have also been suggested as a first option in patients with C-ALCL developing extracutaneous disease. Consistently, in our study, most patients were treated upfront with this modality. Although the majority

Table 1. Clinical characteristics of patients with pcCD30⁺LPDs who developed extracutaneous disease

Characteristic	C-ALCL (n = 30)	LyP (n = 13)	Overall (N = 43)
Sex (male:female)	21:9	10:3	31:12
Age at diagnosis, y			
Median	56	46	53
Range	26-79	31-77	26-79
Initial extent			
Solitary (T1)	16 (54)	0 (0)	16 (37)
Localized (T2)	7 (23)	2 (15)	9 (21)
Generalized (T3)	7 (23)	11 (85)	18 (42)
Initial therapy for cutaneous lesions			
RT	12 (40)	0 (0)	12 (28)
CHOP	5 (17)	0 (0)	5 (12)
MTX	2 (7)	2 (15)	4 (9)
UVB/PUVA	1 (3)	1 (8)	2 (5)
Excision	7 (23)	0 (0)	7 (16)
Expectative	3 (10)	10 (77)	13 (30)
Initial response rates for cutaneous lesions	25 (83)	4 (31)	29 (67)
CR	2 (7)	7 (54)	9 (21)
PR	3 (10)	2 (15)	5 (12)
NR			
Median time to extracutaneous relapse (range), mo	27 (5-264)	60 (7-230)	35 (5-264)
TNM classification: node			
N1	11 (37)	2 (15)	13 (30)
N2	12 (40)	8 (62)	20 (47)
N3	7 (23)	3 (23)	10 (23)
TNM classification: metastases	24 (80)	8 (62)	32 (74)
M0	6 (20)	5 (38)	11 (26)
M1			
Therapy			
Anthracycline-based chemotherapy (+RT/SCT*)	25 (83)	9 (69)	34 (79)
RT	3 (10)	1 (8)	4 (9)
None†	2 (7)	3 (23)	5 (12)
Results			
CR	19 (63)	7 (54)‡	26 (61)
PR	3 (10)	1 (8)	4 (9)
NR	8 (27)	5 (38)	13 (30)
Current status			
Alive without disease	11 (37)	6 (46)	17 (40)
Alive with disease	2 (6)	2 (15)	4 (9)
Died of lymphoma	14 (47)	5 (39)	19 (44)
Died of other cause	3 (10)	0 (0)	3 (7)

Table 1. (continued)

Characteristic	C-ALCL (n = 30)	LyP (n = 13)	Overall (N = 43)
Median follow-up (range), mo	63.5 (12-325)	134 (14-360)	81 (12-360)
5-y PFS, %§	32	54	39
5-y Cumulative incidence of DSD, %§	51	38.5	47
5-y OS, %§	41	61.5	47

PFS was defined as time between date of response to therapy for first extracutaneous lesion(s) and first event (progressive disease following the European Organization of Research and Treatment of Cancer, International Society for Cutaneous Lymphomas, and United States Cutaneous Lymphoma Consortium consensus guidelines for pcCD30⁺LPDs) or death of any cause. Time intervals of cumulative incidence of DSD were determined with time between date of development of extracutaneous disease and date of death from lymphoma or treatment toxicity, and OS was defined as time between date of development of extracutaneous disease to date of death from any cause. Data are presented as N (%) unless otherwise indicated.

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; M0, no evidence of extracutaneous non–lymph node disease; M1, extracutaneous non–lymph node disease present; MTX, methotrexate; N1, involvement of 1 peripheral lymph node region that drains an area of current or prior skin involvement; N2, involvement of 2 or more peripheral lymph node regions or involvement of any lymph node region that does not drain an area of current or prior skin involvement; N3, involvement of central lymph nodes; SCT, stem cell transplantation; UVB/PUVA, ultraviolet B/psoralen and ultraviolet A.

*SCT included autologous SCT as well as allogeneic SCT.

†Spontaneous regression, refused therapy, or death before start of treatment.

‡CR refers to complete remission of extracutaneous localizations.

§After extracutaneous development.

of patients respond to anthracycline-based therapies, ~40% have poor results, which indicates that survival outcomes of these patients need to be improved by optimization of new treatment algorithms (Table 2). Although RT is already suggested as a suitable treatment option in patients with localized lesions and a solitary regional involved lymph node, and we confirmed superior survival in our study, only few patients actually received RT.

Recent studies reported promising results with brentuximab vedotin (BV) as first- and second-line treatment of systemic ALCL.[16-21] This led to an approval by the US Food and Drug Administration for BV + cyclophosphamide, doxorubicin, and prednisone as a first-line treatment option in systemic ALCL and subsequent incorporation into the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology.[18,22] Several studies also report high response rates of BV (monotherapy) in patients with pcCD30⁺LPDs, including patients with relapsed and extracutaneous C-ALCL.[23-25] However, BV is expensive, cumulative neuropathy is a frequent adverse event and long-term effects are still unknown. Furthermore, most BV studies evaluated heterogeneous patient groups, impeding adequate analyses of survival outcomes for specific cutaneous T-cell lymphoma subtypes.

In the current study, we showed that prognosis of patients with a pcCD30⁺LPD who develop extracutaneous localizations corresponds with ALK-negative systemic ALCL and provides a benchmark for novel targeted therapies. Given the therapeutic success in ALK-negative systemic ALCL, BV-based regimens should be considered in patients with a pcCD30⁺LPD who develop extracutaneous localizations. RT may suffice in patients with localized lesions and a solitary regional involved lymph node (supplemental Figure 2).

Table 2. Treatment responses in patients with C-ALCL or LyP developing extracutaneous disease (N = 43)

Therapy	C-ALCL (n = 30)				LyP (n = 13)				Overall (N = 43)					
	N	CR	Relapse skin limited	Systemic relapse	N	CR*	Relapse skin limited (%)	Systemic relapse	N	CR	Relapse (%)	PFS5 (%)	DSD5 (%)	OS5 (%)
Anthracycline-based chemotherapy	25	16/25 (64)	3/16 (19)	6/16 (38)	9	5/9 (56)	3/5 (60)	0/5 (0)	34	21/34 (62)	12/21 (57)	34	46	46
RT	3	3/3 (100)	2/3 (67)	0/3 (0)	1	1/1 (100)	1/1 (100)	0/1 (0)	4	4/4 (100)	3/4 (75)	100	0	100
No therapy	2	0/2 (0)	—	—	3	1/3 (33)	1/1 (100)	0/1 (0)	5	1/5 (20)	1/1 (100)	20	80	20
Total	30	19/30 (63)	5/19 (26)	6/19 (32)	13	7/13 (54)	5/7 (71)	0/7 (0)	43	26/43 (61)	16/26 (62)	39	47	47

Data are presented as n/N (%) unless otherwise indicated.
DSD5, five-year cumulative incidence of DSD.
*CR refers to complete remission of extracutaneous localizations.

Authorship

Contribution: R.C.M., R.W., J.S.P.V., P.M.J., L.A.D., M.H.V., and K.D.Q. designed the research and wrote the paper; M.W.B., E.R.M.d.H., B.H., M.M.v.R., C.J.G.S., and J.C.J.M.V. contributed to the acquisition of the data; H.P. performed and wrote statistical analyses; and all authors contributed to the concept and design of the study and approved the final version of the manuscript.

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Footnote

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TO THE EDITOR:

Multiple *BCL2* mutations cooccurring with Gly101Val emerge in chronic lymphocytic leukemia progression on venetoclax

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Venetoclax is an oral, highly selective BCL2 inhibitor approved as monotherapy or in combination with rituximab or obinutuzumab in chronic lymphocytic leukemia (CLL).[1-4] Despite complete response rates of up to 50%,[1,4,5] secondary resistance is the most frequent cause of treatment failure.[6] Resistance mechanisms that have been observed to date in CLL patients treated with venetoclax include (1) early outgrowth of clones with complex karyotype, mutations in *BTG1*, and aberrations of *CDKN2A/B*[7,8]; (2) the acquisition of a *BCL2* mutation (Gly101Val) that reduces venetoclax binding to BCL2[9,10]; and (3) overexpression of other pro-survival proteins BCL-XL and MCL1.[9,11] An important observation in all of these scenarios is the subclonality of the mutation-bearing cells within the resistant CLL tumor compartment.[9,11] Indeed, the proportion of both the *BCL2* Gly101Val resistance mutation and MCL1-overexpressing CLL cells have been reported to vary widely from a minor subclone through to the majority of the tumor compartment.[9,11] Moreover, different venetoclax resistance mechanisms (including BCL-XL overexpression and *BCL2* Gly101Val mutations) have been observed in independent CLL subpopulations within the same patient.[9] Given the observed subclonality of the *BCL2* Gly101Val mutation in patients to date and therefore the possibility of additional resistance mechanisms occurring specifically in this subgroup (including a recently described candidate *BCL2* resistance mutation Asp103Tyr[10]), we investigated patients with progressive CLL on venetoclax harboring subclonal *BCL2* Gly101Val mutations for the presence of additional acquired *BCL2* resistance mutations to further explain the clinical resistance of the disease in these patients.

Eleven patients with progressive CLL with *BCL2* Gly101Val mutations were identified by sensitive allele-specific droplet digital polymerase chain reaction (ddPCR)[9] from among a cohort of 67 patients with heavily pretreated relapsed CLL treated with venetoclax on 3 early-phase clinical trials at our institutions.[8] Seven of these patients were described in the original report of *BCL2* Gly101Val mutations[9]; 4 patients had newly detected Gly101Val mutations in disease progression samples subsequently (supplemental Material, available on the *Blood* Web site). Using sample tumor burden assessed by flow cytometry and variant allele frequency (VAF) quantitation determined by ddPCR, the proportion of the CLL tumor compartment harboring *BCL2*