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Systemic rituximab for the treatment of the indolent forms of primary cutaneous B-cell lymphomas: Data from the Spanish Primary Cutaneous Lymphoma Registry

To the Editor: Primary cutaneous follicle center B-cell lymphomas (PCFCLs) and primary cutaneous marginal zone B-cell lymphomas (PCMZLs) have an indolent clinical course but a high rate of skin recurrences. Rituximab has been used in cases where local treatment is not indicated, but most publications are limited to isolated cases or short series of patients[1-4] (Supplemental Tables I and II, available via Mendeley at https://doi.org/10.17632/83r5x758gh.2).

This study evaluated the clinical response and tolerability of systemic rituximab as monotherapy in a prospectively monitored cohort of patients from the Spanish Primary Cutaneous Lymphoma Registry (RELCP).

The study included 54 patients (17 women), 29 with PCFCL and 25 with PCMZL. Patient characteristics are summarized in Table I. The median age at diagnosis was 54 years, and median follow-up was 90 months.

All patients received 4 intravenous weekly infusions of rituximab at a standard dose of 375 mg/m^2/d. The overall response rate, complete response (CR), partial response, stable disease, time to progression, progression-free survival (PFS), and time to next treatment (TTNT) were evaluated according to the Olsen criteria.[5] The overall response rate was 98%. There were 37 patients (68%) who achieved a CR (21 PCFCL and 16 PCMZL), 16 (30%) showed a partial response, and 1 (2%) had stable disease. Among 5 patients with nodal involvement, 4 achieved CR and 1 partial response. There were no differences in overall response rate or CR between PCFCL and PCMZL. This is in contrast with previous observations suggesting a lower response rate for PCMZL.[1,2]

Cutaneous relapse or progression occurred in 24 patients (44%), 12 with PCFCL and 12 with PCMZL, with a median time to progression of 11 months. Of these, 16 were retreated with systemic rituximab, with a median of 4 additional infusions. Median PFS after the initial rituximab treatment was 62 months (78 for PCFCL and 58 for PCMZL). These differences did not reach statistical significance ($P = .1719$) (Fig 1). Median TTNT was 62 months. No associations were found in Cox regression models in PFS or TTNT regarding type of lymphoma, sex, age, extent of lesions, or previous treatment with intralesional rituximab.

Treatment was well tolerated. The most frequent adverse events were grade 1 and 2 infusion reactions and transient inflammatory changes over the skin lesions. Some patients showed inflammatory reactions over apparently unaffected skin suggesting occult extension beyond the affected areas.

To the best of our knowledge, this study represents the largest series published. Because it originates from a national multicenter prospective registry, these results probably represent the current

Table I. Characteristics of patients treated with systemic rituximab

Characteristics	Total (N = 54)	PCFCL (n = 29)	PCMZL (n = 25)	*P* value
Sex, No. (%)				.609
Male	37 (69)	19 (66)	18 (72)	
Female	17 (31)	10 (34)	7 (28)	
Age at diagnosis, median (IQR), y	54 (41-62)	53 (41-59)	55 (37-62)	.9042
Previous treatment with intralesional rituximab, No. (%)	9 (17)	6 (21)	3 (12)	.316
Stage before treatment rituximab, No. (%)				.802
T1	7 (13)	4 (14)	3 (12)	
T2	20 (37)	12 (41)	8 (32)	
T3	27 (50)	13 (45)	14 (56)	
N0	49 (91)	26 (90)	23 (92)	.887
N1	3 (5)	2 (7)	1 (4)	
N2	1 (2)	0 (0)	1 (4)	
N3	1 (2)	1 (3)	0 (0)	
Response, No. (%)				.552
Complete response	37 (68)	21 (72)	16 (64)	
Partial response	16 (30)	7 (24)	9 (36)	
Stable disease	1 (2)	1 (4)	0 (0)	
Relapse, No. (%)				.6254
No	30 (56)	17 (59)	13 (52)	
Yes	24 (44)	12 (41)	12 (48)	
Time to progression, median (IQR), mo	11 (7-21)	12 (9-34)	9 (5-13)	.1782
Progression-free survival, median (SE), mo	62 (16)	78 (29)	58 (27)	.1719
Time to next treatment, median (SE), mo	62 (17)	85 (33)	60 (NA)	.3452
Adverse events, No. (%)				
Inflammatory reactions at lymphoma sites	16 (30)	11 (38)	5 (20)	.1502
Systemic symptoms*	17 (32)	9 (30)	8 (32)	>.99
Grade 1	14 (26)	7 (24)	7 (28)	
Grade 2	2 (4)	1 (3)	1 (4)	
Grade 3	1 (2)	1 (3)	0 (0)	
Follow-up, median (IQR), mo	90 (41-171)	83 (39-181)	92 (61-166)	.9726
Current status, No. (%)				.243
Alive without disease	38 (70)	19 (66)	19 (76)	
Alive with disease	11 (20)	5 (17)	6 (24)	
Lost follow-up	2 (4)	2 (7)	0	
Died of others causes	2 (4)	2 (7)	0	
Died of lymphoma	1 (2)	1 (3)	0	

IQR, Interquartile range; *NA*, not available; *No.*, number; *PCFCL*, primary cutaneous follicle center lymphoma; *PCMZL*, primary cutaneous marginal zone lymphoma; *SE*, standard error.

*Systemic symptoms: grade 1, pruritus, erythema, urticaria; grade 2, nausea, vomiting, chest oppression, diarrhea, angioedema; grade 3, dyspnea, dysarthria, dysphonia, weakness, confusion.

use of rituximab in this setting. Retrospective analysis could potentially decrease data quality, but therapy and evolution were precisely recorded in patient medical records. The limited sample implies a low power to detect adverse events. However, the available large amount of safety data on rituximab supports our results.

In summary, this study demonstrated a high response rate and a good tolerability after 4 infusions of systemic rituximab for the treatment of patients with PCFCL and PCMZL. Data from previously reported experience indicate that there seems to be no further benefits of additional rituximab infusion in terms of PFS.[1,4] Although skin relapses are frequent, a significant number of patients can achieve long-lasting clinical responses.

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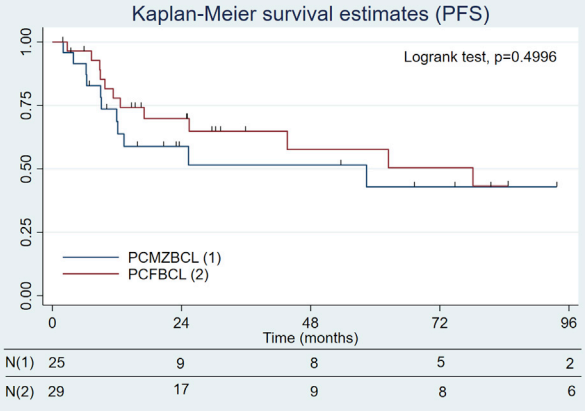

Fig 1. Kaplan-Meier curve shows progression-free survival (*PFS*) in patients with primary cutaneous follicle center B-cell lymphomas (*PCFCLs*) and primary cutaneous marginal zone B-cell lymphomas (*PCMZLs*).

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Risk assessment of outpatient dermatology practice in the setting of the COVID-19 pandemic

To the Editor: Severe acute respiratory syndrome coronavirus 2 has had a mortality rate of 2.2% in China and 7.2% in Italy. Mortality and severity of infection are associated with older age and comorbidities.[1] Infectivity is estimated at 2% to 3.58% of exposures. Health care workers, representing up to 20% of those infected, are at elevated risk. The high rates of infectivity and mortality raise questions on how outpatient clinics can reduce risk. We created a model to assess the weekly risk of exposure in a dermatology practice.

In the United States, testing is limited in many places to patients who are highly symptomatic. The largest study to date, which mainly focused on testing symptomatic individuals from Wuhan, reported 81% to have mild disease and 19% to have severe illness.[1] Additionally, many may be completely asymptomatic. In New York on April 27, 2020, the reported number of positive cases was 298,004. The same day, a seroprevalence study showed a positivity rate of 14.9% in the state of 19.45 million people, roughly translating to 2,898,050 infections. These studies suggest that current reporting may be capturing only 10% to 20% of all infections. There are surmounting data that the number of infections is far greater than reported.

To help dermatologists better grasp the impact of COVID-19, we created 2 models: a dermatologist practicing in Chicago (city population of 2,700,000) and one practicing in a metropolitan area of 100,000. The model assumes each physician sees 145 patients per week, which is the national average.[2] The model displays a range that assumes the ratio of symptomatic-to-asymptomatic infections is 1:4 or 1:9, which are based on data from Wuhan and New York, respectively. The range also uses current data that the sensitivity of the polymerase chain reaction test may be as low as 70% or as high as 95%.[3] The number of asymptomatic or mildly symptomatic patients in a population and the number of these patients a dermatologist is likely to encounter in a given week are shown for Chicago (Table I) and a metropolitan area of 100,000 (Table II). When there are 4425 average daily new positive cases in Chicago and 165 in the smaller metropolitan area, a conservative estimate would suggest that a dermatologist could expect to encounter 1 mildly symptomatic or asymptomatic patient with COVID per week.

Table I. Expected exposure rates in the city of Chicago

Number of positive cases	Number of undiagnosed, mild, or minimally symptomatic cases, range	Patient exposure, weekly, range
100	421-1286	0.02-0.071
500	2105-6429	0.11-0.35
1000	4211-12,857	0.23-0.69
4425	**18,632-56,893**	**1.00-2.25**
5000	21,053-64,286	1.13-3.45
10,000	42,105-128,571	2.26-6.90
50,000	210,526-642,587	11.31-34.52
100,000	421,053-1,285,714	22.61-69.05

Bold represents when the threshold when a dermatologist can anticipate to encounter at least one active COVID patient per week.

Table II. Expected exposure rates in a metropolitan area of 100,000 people

Number of positive cases	Number of undiagnosed, mild, or minimally symptomatic cases, range	Patient exposure, weekly, range
10	42-129	0.06-0.19
50	211-643	0.31-0.93
100	421-1286	0.61-1.86
165	**695-2121**	**1.00-1.08**
500	2105-6429	3.05-9.32
1000	4211-12,857	6.11-18.64
5000	21,053-64,286	30.53-93.21
10,000	42,105-128,571	61.05-186.43

Bold represents when the threshold when a dermatologist can anticipate to encounter at least one active COVID patient per week.

The virus is transmitted through airborne aerosols, including speaking, which can travel for at least 6 feet.[3] Furthermore, viral loads are similar in both symptomatic and asymptomatic individuals.[4] Surgical masks can decrease transmission by 75%,[5] and N95 masks are even more protective. However, depending on the type and fit of PPE, dermatologists and their staff could be exposed to the virus if a patient with COVID is seen.

If in-person clinic volumes return to prequarantine levels and if new infections continue in the community, exposure to COVID-positive patients is inevitable. However, there are steps we can take to mitigate the risk. Screening patients for symptoms and recent close contacts with COVID is essential. Universal PPE for dermatologists and their staff, ideally N95 masks, is also needed.