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Chronic Obstructive Pulmonary Disease and Previous Pneumonia have an impact on infectious complications in patients with Chronic Lymphocytic Leukemia treated with Acalabrutinib and Zanubrutinib: a Multicentre SEIFEM Study.

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INTRODUCTION

Infections remain a major cause of morbidity and mortality in patients with Chronic Lymphocytic Leukemia (CLL). Although the advent of targeted therapies has reduced infection rates, many patients, often elderly, heavily pretreated, and burdened with comorbidities, still experience serious infectious complications.

METHODS

This multicenter retrospective real-world study aimed to describe infectious events in CLL patients treated with second-generation Bruton's Tyrosine Kinase inhibitors (BTKis)—Acalabrutinib (Acala) and Zanubrutinib (Zanu)—and to identify key infection-related risk factors.

RESULTS

We analyzed 460 patients in the period 2019-2024 from 15 hematological centers: 324 received Acala and 136 Zanu. Patients treated with Zanu were older and had more frequent TP53 mutations, renal and pulmonary comorbidities, advanced Rai stage, and prior treatments (Table 1 and Table 2)

During Acala therapy, 164 non-COVID infections occurred in 110 patients (34%), with an event rate of 0.51; 54.3% involved the respiratory tract. In the Zanu group, 71 infections occurred in 49 patients (36%), with a similar rate (0.52); 46.5% were respiratory.

Among Acala-treated patients, 48 infections were grade 3–4, occurring in 42 patients (13.0%; rate 0.14), including 32 respiratory infections and 9 cases of sepsis

Pathogens were identified in 21 cases: 12 bacterial (4 E. coli), 5 viral, and 4 fungal (3 Aspergillus, 1 Candida glabrata). In the Zanu group, 15 grade 3–4 infections occurred in 13 patients (9.6%; rate 0.11), including 8 respiratory infections and 3 cases of sepsis. Pathogens were isolated in 6 cases (5 bacterial, 1 viral).

Infections occurred earlier with Zanu (median 4.5 months vs 8.2 months with Acala; p=0.068), and grade 3–4 infections appeared significantly sooner (3.1 vs 7.8 months; p=0.025).

In the Acala group, risk factors for infections of any grade included age, diabetes, chronic obstructive pulmonary disease (COPD), CrCl <70 mL/min, comorbidity index (CIRS), prior lines of therapy, and history of infections or pneumonia in the previous 12 months. For Zanu, significant risk factors were diabetes, Rai stage, and prior infections or pneumonia.

For grade 3–4 infections, the only significant predictors were COPD and prior pneumonia for Acala (p<0.001), and prior pneumonia for Zanu (p<0.001). Stratifying patients by COPD and previous infection yielded three distinct risk groups (p<0.001); the cumulative 1-year incidence of infection reached 89.4% in those with both risk factors (Figure 1).

The 5-year overall survival (OS) was 71.2% with Acala (35 deaths, 16 infection-related) and 80.0% with Zanu (9 deaths, 4 infection-related). BTKi discontinuation due to infections occurred in 38 Acala patients (34.5%), with 7 permanent discontinuations (6 pneumonia, 1 sepsis); 6 of these patients died. In the Zanu group, 12 patients (24.5%) discontinued due to infections, with 1 permanent case related to pneumonia.

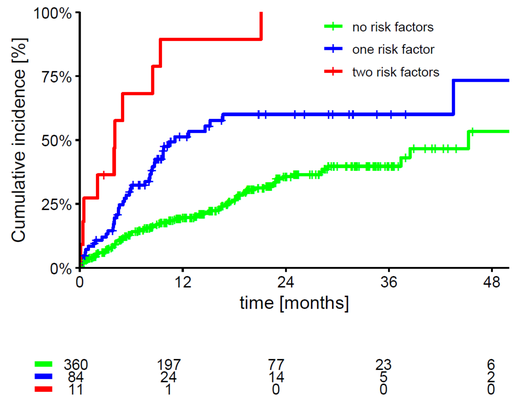
Table 1: Clinico-biological characteristics of patients treated with Acalabrutinib.

	Acala (n=324)	No infection (n=214)	Yes infection (n=110)	
SEX				0.88
M	208 (64.2)	138 (64.5)	70 (63.6)	
F	116 (35.8)	76 (35.5)	40 (36.4)	
AGE AT DIAGNOSIS	67 (59-74)	67.5 (57.9-74.4)	67.2 (59.4-73.6)	0.92
AGE AT BTKi	74 (65-80)	73.3 (64.5-78.9)	74.5 (68.3-82.0)	0.046
SMOKING				0.14
No	246 (77.1)	168 (79.6)	78 (72.2)	
Yes	73 (22.9)	43 (20.4)	30 (27.8)	
DIABETES				0.015
No	273 (84.8)	188 (88.3)	85 (78.0)	
Yes	49 (15.2)	25 (11.7)	24 (22.0)	
BPCO				<0.001
No	290 (89.8)	200 (93.9)	90 (81.8)	
Yes	33 (10.2)	13 (6.1)	20 (18.2)	
DRUGS FOR BPCO				0.001
No	295 (93.4)	201 (96.6)	94 (87.0)	
Yes	21 (6.6)	7 (3.4)	14 (13.0)	
CREATININE CLEARANCE ≤ 70 ml/min				0.039
No	177 (54.8)	126 (58.9)	51 (46.8)	
Yes	146 (45.2)	88 (41.1)	58 (53.2)	
CIRS	5 (3-8)	4 (2-7)	6 (4-8)	<0.001
ELEVATED LDH				0.79
No	175 (54.5)	115 (54.0)	60 (55.6)	
Yes	146 (45.5)	98 (46.0)	48 (44.4)	
ELEVATED BETA2				0.29
No	73 (28.6)	52 (30.8)	21 (24.4)	
Yes	182 (71.4)	117 (69.2)	65 (75.6)	
RAI STAGE				0.33
0	3 (0.9)	2 (0.9)	1 (0.9)	
I	21 (6.5)	17 (8.0)	4 (3.7)	
II	131 (40.7)	90 (42.3)	41 (37.6)	
III	66 (20.5)	38 (17.8)	28 (25.7)	
IV	101 (31.4)	66 (31.0)	35 (32.1)	
BINET STAGE				0.10
A	41 (12.8)	33 (15.5)	8 (7.4)	
B	124 (38.6)	82 (38.5)	42 (38.9)	
C	156 (48.6)	98 (46.0)	58 (53.7)	
IGHV				0.59
Mutated	85 (29.3)	54 (28.3)	31 (31.3)	
Unmutated	205 (70.7)	137 (71.7)	68 (68.7)	
TP53				0.20
WT	254 (84.7)	163 (82.7)	91 (88.3)	
Mutated	46 (15.3)	34 (17.3)	12 (11.7)	
PREVIOUS THERAPY LINES				0.011
0	234 (73.4)	165 (78.2)	69 (63.9)	
1	68 (21.3)	39 (18.5)	29 (26.9)	
≥ 2	17 (5.3)	7 (3.3)	10 (9.3)	
INFECTIONS IN THE PREVIOUS 12 MONTHS				0.003
No	242 (77.6)	170 (82.5)	72 (67.9)	
Yes	70 (22.4)	36 (17.5)	34 (32.1)	
PNEUMONIA IN THE PREVIOUS 12 MONTHS				<0.0001
No	269 (87.1)	190 (93.6)	79 (74.5)	
Yes	40 (12.9)	13 (6.4)	27 (25.5)	

Table 2: Clinico-biological characteristics of patients treated with Zanubrutinib.

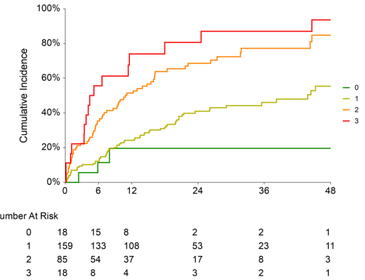
	Zanu (n=136)	No infection (n=87)	Yes infection (n=49)	
SEX				0.61
M	85 (62.5)	53 (60.9)	32 (65.3)	
F	51 (37.5)	34 (39.1)	17 (34.7)	
AGE AT DIAGNOSIS	70 (58-78)	72.1 (57.8-79.4)	68.0 (58.4-75.0)	0.13
AGE AT BTKi	76 (67-83)	78.2 (66.2-83.7)	74.2 (70.0-81.5)	0.67
SMOKING				0.22
No	113 (84.3)	75 (87.2)	38 (79.2)	
Yes	21 (15.7)	11 (12.8)	10 (20.8)	
DIABETES				0.048
No	114 (83.8)	77 (88.5)	37 (75.5)	
Yes	22 (16.2)	10 (11.5)	12 (24.5)	
BPCO				0.41
No	113 (83.1)	74 (85.1)	39 (79.6)	
Yes	23 (16.9)	13 (14.9)	10 (20.4)	
DRUGS FOR BPCO				0.25
No	122 (89.7)	80 (92.0)	42 (85.7)	
Yes	14 (10.3)	7 (8.0)	7 (14.3)	
CREATININE CLEARANCE ≤ 70 ml/min				0.074
No	61 (44.9)	44 (50.6)	17 (34.7)	
Yes	75 (55.1)	43 (49.4)	32 (65.3)	
CIRS	5 (3-7)	5 (3-7)	5 (4-7)	0.46
ELEVATED LDH				0.12
No	73 (53.7)	51 (58.6)	22 (44.9)	
Yes	63 (46.3)	36 (41.4)	27 (55.1)	
ELEVATED BETA2				0.18
No	34 (28.1)	24 (32.4)	10 (21.3)	
Yes	87 (71.9)	50 (67.6)	37 (78.7)	
RAI STAGE				0.026
0	4 (2.9)	3 (3.4)	1 (2.0)	
I	20 (14.7)	14 (16.1)	6 (12.2)	
II	34 (25.0)	25 (28.7)	9 (18.4)	
III	40 (29.4)	29 (33.3)	11 (22.4)	
IV	38 (27.9)	16 (18.4)	22 (44.9)	
BINET STAGE				0.21
A	16 (11.8)	13 (14.9)	3 (6.1)	
B	45 (33.1)	30 (34.5)	15 (30.6)	
C	75 (55.1)	44 (50.6)	31 (63.3)	
IGHV				0.25
Mutated	31 (24.0)	17 (20.7)	14 (29.8)	
Unmutated	98 (76.0)	65 (79.3)	33 (70.2)	
TP53				0.52
WT	96 (75.0)	60 (73.2)	36 (78.3)	
Mutated	32 (25.0)	22 (26.8)	10 (21.7)	
PREVIOUS THERAPY LINES				0.63
0	77 (57.0)	51 (59.3)	26 (53.1)	
1	43 (31.9)	27 (31.4)	16 (32.7)	
≥ 2	15 (11.1)	8 (9.3)	7 (14.3)	
INFECTIONS IN THE PREVIOUS 12 MONTHS				0.026
No	113 (84.3)	77 (89.5)	36 (75.0)	
Yes	21 (15.7)	9 (10.5)	12 (25.0)	
PNEUMONIA IN THE PREVIOUS 12 MONTHS				0.009
No	119 (90.2)	80 (95.2)	39 (81.3)	
Yes	13 (9.8)	4 (4.8)	9 (18.8)	

Figure 1. Stratification of patients according to the two risk factors for infections COPD and previous infections in the last 12 months: none risk factor (group 0), one of the two risk factors (group 1), both the risk factors (group 2), p <0.001.



COVID-19 status was available for 455 patients. We documented 84 cases (26.2%) in the Acala group and 18 (13.4%) in the Zanu group. Nearly half of these patients also developed other infections (46.4% with Acala, 50% with Zanu). Hospitalization was required in 10 Acala-treated patients (11.9%) and 5 Zanu-treated patients (27.8%; p=0.08). COVID-19 was the cause of death in 3 cases, all in Acala group.

Figure 2. Venetoclax Infectious Risk Score (VIRS) stratification of patients according to the risk factors for infections (COPD, previous infections in the last 12 months and previous treatments). Very low-risk patients (no risk factors, RS), low-risk patients (1 RS), intermediate-risk patients (2 RS), high-risk patients (3 RS).



CONCLUSIONS

This large real-world study demonstrates a moderate rate of infections, mostly grade 1–2, during BTKi therapy. COPD and prior pneumonia emerged as key risk factors for severe infections, consistent with previous SEIFEM data on venetoclax plus anti-CD20 regimens (Autore et al., AJH 2024; Figure 2). Our findings support the need for closer monitoring and potentially tailored treatment strategies in patients with these specific risk factors.