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RESEARCH ARTICLE

Pneumonia in patients with chronic lymphocytic leukemia treated with venetoclax-based regimens: A real-world analysis of Polish Adult Leukemia Group (PALG)

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Abstract

Background: Patients with chronic lymphocytic leukemia (CLL) are susceptible to infections that can affect their clinical outcomes.

Aims: To assess: (1) the incidence of pneumonia in CLL patients treated with venetoclax-based regimens in a real-world setting, (2) the risk factors for event-free survival (EFS), and (3) overall survival (OS).

Methods: This multicenter study included 322 patients from eight centers. Univariable and multivariable analyses (MVA) were performed, having the development of pneumonia during venetoclax-based treatment and OS as outcomes.

Results: The most common complication was neutropenia (59%). During treatment with venetoclax-based regimens, 66 (20%) of patients developed pneumonia: 50 (23%) patients in the rituximab plus venetoclax (R-VEN) group, 13 (16%) patients in the obinutuzumab plus venetoclax (O-VEN) group ($p = 0.15$). Chronic obstructive pulmonary

disease (COPD)/asthma, splenomegaly, elevated creatinine, and anemia <8 g/dL were the risk factors for EFS in MVA (hazard ratio [HR] = 2.08, 95% confidence interval [CI], 1.16–3.74, $p = 0.014$; HR 1.73, 95% CI, 1.08–2.78, $p = 0.02$; HR 2.13, 95% CI, 1.10–4.11, $p = 0.03$, HR 3.58, 95% CI, 2.18–5.89, $p < 0.001$, respectively). Relapsed/refractory (R/R) CLL patients treated with R-VEN with pneumonia had worse OS than those without ($p < 0.001$). In patients treated with O-VEN, median OS did not differ between patients with and without pneumonia ($p = 0.45$).

Conclusions: Our real-world study showed that pneumonia during venetoclax treatment occurs more frequently than reported in registration trials and has a negative impact on OS, especially in patients with R/R CLL treated with R-VEN. Neutropenia is not a risk factor for pneumonia.

KEYWORDS
CLL, infection, overall survival, pneumonia, venetoclax

1 | BACKGROUND

Patients with chronic lymphocytic leukemia (CLL) are susceptible to infections that can affect clinical outcomes and contribute to a poor prognosis. The increased risk of severe infections is due to the underlying disease, comorbidities, and applied treatment.

Most infectious complications are associated with immunochemotherapy, which has a very limited role in the treatment of CLL in the current era [1].

Targeted therapies including Bruton's kinase inhibitors (BTKi) and Bcl-2 inhibitors (venetoclax) constitute now the standard of care for most patients with CLL, either as a first-line or subsequent treatment.

Fixed-duration therapy with venetoclax and anti-CD20 monoclonal antibody, obinutuzumab, was associated with a 60% reduction in the risk of progression or death compared to treatment with chlorambucil and obinutuzumab. The 6-year follow-up of the CLL14 trial demonstrated the efficacy of this combination in untreated CLL patients regardless of TP53 or IGHV mutation status [2]. Similarly, in patients with relapsed/refractory (R/R) CLL, combination treatment with venetoclax and rituximab had a high response rate, including those with unfavorable genetic patterns such as 17p deletion [3]. Therefore, venetoclax-based regimens are widely used in the treatment of CLL and, as a fixed-duration therapy, are an attractive option for both the first and subsequent lines.

Both the CLL-14 trial, and the MURANO trial, have shown that venetoclax treatment has an acceptable safety profile [4, 5].

In the MURANO trial pneumonia was observed in 9.3% of patients treated with rituximab plus venetoclax (R-VEN). In the CLL-14 trial, only 4.7% of patients treated with obinutuzumab plus venetoclax (O-VEN) had pneumonia. According to the European Society for Medical Oncology (ESMO) guidelines, antibiotic and antiviral prophylaxis is not recommended as routine practice for all treated patients with CLL. Only patients with recurrent infections or at very high risk of developing infections should receive prophylaxis against pneumocystis pneumonia (PCP). Similarly, routine antifungal prophylaxis is not currently recommended. The National Comprehensive Cancer Network (NCCN) guidelines also indicate that prophylaxis is recommended only in selected groups of patients with CLL, treated mainly with PI3K inhibitors, chemoimmunotherapy with fludarabine or bendamustine and alemtuzumab.

However, outside registration trials, there is insufficient real-world data to estimate the incidence of infections that may affect treatment outcomes.

Pneumonia is one of the key serious adverse events that can have the greatest impact on prognosis.

Therefore, it seems reasonable to assess the occurrence of pneumonia and its predictive factors in the real-world in CLL patients in the context of its impact on treatment outcomes and prognosis.

The aim of this study was to assess the incidence, impact on prognosis and risk factors for pneumonia in CLL patients treated with venetoclax-based regimens at the centers of the Polish Adult Leukemia Study Group (PALG).

2 | METHODS

2.1 | Study population

This retrospective multicenter study was conducted in eight hematological centers associated with the PALG. Data were collected between April 2019 and October 2023. For patients treated with O-VEN, it was first-line therapy. Patients treated with R-VEN constituted the group of patients with R/R CLL. R/R CLL patients were treated in the previous line with chemoimmunotherapy.

Researchers from each participating center provided data on consecutive patients with CLL treated with venetoclax-based regimens between 2019 and 2023. CLL diagnosis and eligibility for treatment were conducted by local researchers in accordance with current

guidelines. The inclusion criteria included: age ≥18 years, confirmed diagnosis of CLL with indications for treatment according to the guidelines of the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2018 criteria, the Cumulative Illness Rating Scale (CIRS) >6 points for newly diagnosed CLL patients treated with O-VEN, R/R CLL after the ≥ first line of treatment (chemotherapy and immunochemotherapy) for patients treated with R-VEN. The exclusion criteria included: transformation of CLL to aggressive non-Hodgkin lymphoma (NHL; Richter's transformation), known history of infection with human immunodeficiency virus (HIV).

The development of pneumonia was reported during treatment with venetoclax-based regimens in patients with CLL and the definition was consistent with the National Cancer Institute Common Terminology Criteria for Adverse Events Assessment, version 5. Due to the retrospective nature of the study only ≥3 grade pneumonia was reported. To eliminate collection bias, other pulmonary complications such as upper respiratory tract infections (sinusitis, tonsillitis, and bronchitis) were not considered as differential factors due to the difficulty in defining them correctly based on retrospective analysis.

This study was performed in accordance with the Wroclaw Medical University Ethics Committee. Approval number: KB71/2024; date of approval: June 27, 2024.

2.2 | Statistical analysis

Numerical data were presented as median with interquartile range (IQR). Descriptive statistics were presented as absolute numbers with percentages. The Kolmogorov–Smirnov (K–S) test was used to assess data distribution. Mann–Whitney *U*-test was applied to compare quantitative data between two groups. Pearson's chi-square analysis or Fisher's exact test was used for intergroup comparison of categorical variables. Time-to-event data described in the manuscript included:

1. Overall survival (OS) was defined for nonpneumonia patients as the time from initiation of venetoclax therapy to death for any reason, whereas for pneumonia patients as the time from pneumonia diagnosis to death for any reason.
2. Event-free survival (EFS) was defined as the time from initiation of venetoclax therapy to the event: pneumonia or death from any reason, whichever occurred first.

OS was compared using a log-rank test between pneumonia and nonpneumonia patients. Odds ratio (OR) was used to assess the risk factors associated with the risk of developing the outcome of interest (independently of the time this happens), and hazard ratio (HR) was used to assess the risk factors associated with the time of outcome development. All ratios were presented with the corresponding 95% confidence intervals (CIs). Logistic regression and Cox regression models were applied for OR and risk factors identified with HR calculation, respectively. Univariable and multivariable analyses (MVA) were performed for all investigated patients and subgroups. Investigated risk factors included: sex, comorbidities (hypertension, chronic obstructive pulmonary disease [COPD], asthma, ischemic heart disease/heart failure [IHD/HF], chronic kidney disease, CIRS, presence of splenomegaly, B symptoms, neutropenia, anemia, creatinine level, hemoglobin level, white blood cells count, platelets count, lactate dehydrogenase [LDH], the CD4/CD8 lymphocyte ratio, β2-microglobulin level, and immunoglobulin IgG level). Variables initially selected based on their associations with increased risk of pneumonia in univariate analysis ($p < 0.10$; univariate analysis), were included for a stepwise regression model.

If a result was missing, the patient's data were excluded from this particular analysis. All calculations were performed for the whole cohort of CLL patients treated with venetoclax-based regimens. Some additional calculations were performed separately: (1) within CLL patients treated with the R-VEN, and (2) within CLL patients treated with the O-VEN.

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3 | RESULTS

3.1 | Baseline characteristics

A total of 322 patients with CLL treated with venetoclax-based regimens in eight hematological centers were included in the study (Table 1). Among these, 214 patients were treated with rituximab–venetoclax regimen as a subsequent treatment line (R/R CLL), while 82 patients were treated with obinutuzumab–venetoclax regimen as a first-line CLL treatment. Twenty-six patients received venetoclax in combination with other agents (including BTKi)—not included in the analysis. Median age upon initiation of venetoclax treatment was 63 years, patients treated with O-VEN were older, with median age 68 years ($p < 0.001$). Most patients were male (62%). The most common comorbidity was hypertension (52%), with a slight predominance in patients treated with O-VEN ($p = 0.05$). Patients treated with the O-VEN regimen had more comorbidities, with a median CIRS score of 7 compared to a median CIRS score of 4 in patients treated with the R-VEN regimen ($p < 0.001$), which reflects the inclusion criteria valid at the time of enrollment. The most common treatment complication was neutropenia (59%), occurring more frequently in patients treated with the R-VEN regimen (68%) compared to 46% in patients during the O-VEN therapy ($p = 0.001$). The second most common complication of treatment was upper respiratory tract infections and pneumonia. During treatment with venetoclax-based regimens, 66 (20%) of patients developed pneumonia: 50 (23%) patients in the R-VEN group, 13 (16%) patients in the O-VEN group ($p = 0.15$). Viral etiology of pneumonia was confirmed in 39 (59%) patients. In two patients, etiology of pneumonia was unknown. The incidence of upper respiratory tract infections was similar among patients treated with the R-VEN and O-VEN regimens, both 32%. COVID-19 was diagnosed in 11% of all patients, with no significant differences between treated patient cohorts. Patients treated with the R-VEN regimen compared to

TABLE 1 Clinical characteristics of patients with chronic lymphocytic leukemia (CLL; treated with rituximab plus venetoclax [R-VEN] vs. obinutuzumab plus venetoclax [O-VEN]).

Variable	All patients with CLL, *n* = 322	Patients with CLL treated with R-VEN, *n* = 214	Patients with CLL treated with O-VEN, *n* = 82	R-VEN versus O-VEN, *p*
Age at start of VEN, median, interquartile range (IQR; years)	63 (56–70)	61 (55–69.0)	68 (61–73)	<0.001
Male, *n* (%)	201 (62)	132 (62)	55 (67)	0.389
Comorbidities				
Hypertension, *n* (%)	166 (52)	103 (48)	51 (62)	0.051
Diabetes mellitus, n (%)	63 (20)	34 (16)	24 (29)	0.013
Chronic obstructive pulmonary disease (COPD)/asthma, *n* (%)	23 (7)	14 (7)	7 (9)	0.593
Stroke/Transient ischemic attack (TIA), *n* (%)	14 (4)	11 (5)	3 (4)	0.600
Supraventricular arrhythmia, *n* (%)	41 (13)	25 (12)	14 (17)	0.256
Coronary artery disease/stable heart failure, *n* (%)	43 (13)	24 (11)	18 (22)	0.023
Bowel disease, *n* (%)	27 (8)	23 (11)	4 (5)	0.103
Chronic kidney disease, *n* (%)	29 (9)	17 (8)	11 (13)	0.174
Venous thromboembolism, *n* (%)	16 (5)	10 (5)	6 (7)	0.404
Vascular disease, *n* (%)	54 (17)	29 (14)	22 (27)	0.009
Thyroid disease, *n* (%)	40 (12)	24 (11)	11 (13)	0.659
Other malignancies, *n* (%)	45 (14)	27 (13)	14 (17)	0.321
Cumulative Illness Rating Scale (CIRS) score	5.0 (2.0–8.0)	4.0 (2.0–8.0)	7.0 (4.0–9.0)	<0.001
CIRS >6, *n* (%)	115 (36)	66 (31)	46 (56)	<0.001
CLL characteristics				
Maximum nodal diameter, median (cm)	3.5 (2.5–5.0)	3.7 (2.8–5.0)	3.5 (2.5–5.3)	0.953
Splenomegaly, *n* (%)	184 (57)	122 (62)	51 (62)	0.967
Autoimmune hemolysis, *n* (%)	33 (10)	24 (11)	4 (5)	0.104
Del 17p, *n* (%)	26 (8)	19 (10)	4 (8)	0.624
Del 11q, *n* (%)	63 (20)	49 (23)	9 (11)	
Lines of treatment before venetoclax, median	1 (0–2)	2 (1–3)	0 (0–0)	<0.001
Complications				
Upper respiratory tract infection, *n* (%)	96 (30)	69 (32)	26 (32)	0.910
Pneumonia, *n* (%) Viral etiology, *n* (%) Nonviral etiology, *n* (%)	66 (20) 39 (59) 25 (38)	50 (23) 32 (64) 17 (34)	13 (16) 6 (46) 6 (46)	0.152 0.079 0.978
Neutropenia, *n* (%)	190 (59)	144 (68)	38 (46)	0.001
Anemia (Hb < 8 g/dL), *n* (%)	39 (12)	31 (15)	2 (2)	0.002
Tumor Lysis Syndrome (TLS), *n* (%)	40 (12)	13 (6)	9 (11)	0.150
Diarrhea/intestinal infection, *n* (%)	24 (7)	16 (7)	6 (7)	0.963
Urinary tract infection, *n* (%)	4 (1)	2 (1)	1 (1)	1.000[a]
Sepsis, *n* (%)	4 (1)	3 (1)	1 (1)	1.000[a]
COVID-19, *n* (%)	34 (11)	23 (11)	7 (9)	0.573
Laboratory measures at start of VEN				
White blood cells (G/L) $\times 10^9$/L; median, IQR	65.2 (20.1–146.2)	60.4 (20.1–144.2)	68.4 (22.6–136.9)	0.820
Lymphocytes (G/L) $\times 10^9$/L; median, IQR	32.8 (5.7–98.3)	34.7 (5.5–110.7)	33.5 (8.0–86.9)	
Hemoglobin (g/dL) median, IQR	11.3 (9.5–12.9)	11.4 (9.6–12.9)	11.9 (9.7–13.0)	0.257

(Continues)

TABLE 1 (Continued)

Variable	All patients with CLL, $n = 322$	Patients with CLL treated with R-VEN, $n = 214$	Patients with CLL treated with O-VEN, $n = 82$	R-VEN versus O-VEN, p
Platelets (G/L) $\times 10^9$/L; median, IQR	124 (81–165)	120 (77–163)	132 (89–175)	0.102
Creatinine (mg/dL); median, IQR	0.91 (0.80–1.10)	0.92 (0.81–1.13)	0.94 (0.77–1.10)	0.743
Lactate dehydrogenase (LDH; U/L); median, IQR	244 (201–320)	259 (218–322)	216 (181–274)	<0.001
Endothelial Activation and Stress Index (EASIX) score; median, IQR	2.0(1.3–3.9)	2.3 (1.4–4.2)	1.61 (1.1–3.2)	0.050
Lymphocytes CD4/CD8 ratio; median, IQR	1.22 (0.92–1.76)	1.23 (0.94–1.58)	1.46 (1.0–2.0)	0.224
β2-Microglobulin (mg/L); median, IQR	4.0 (2.8–5.4)	4.4 (2.9–5.9)	3.2 (2.7–4.1)	0.01
Immunoglobulin IgG (g/L); median, IQR	6.1 (4.4–8.3)	5.8 (4.1–7.9)	7.0 (5.0–9.4)	0.009
Clinical outcome, death, n (%)	47 (15)	35 (18)	5 (6)	0.012

[a]Fisher's exact test.

patients treated with the O-VEN regimen were characterized by significantly higher median LDH (259 vs. 216, $p < 0.001$), β2-microglobulin (4.4 vs. 3.2, $p = 0.01$), lower median immunoglobulin IgG levels (5.8 vs. 7.0, $p = 0.009$), and higher the Endothelial Activation and Stress Index (EASIX) score (2.3 vs. 1.6, $p = 0.05$). Deaths were reported in 47 (15%) patients: in 35 (18%) patients treated with the R-VEN regimen, in five (6%) patients treated with the O-VEN regimen, and in seven (30%) treated with another venetoclax combination therapies.

The cumulative incidence of pneumonia was 20% in the entire cohort, with 23.5% and 15.9% in patients treated with R-VEN and O-VEN, respectively.

3.2 | Clinical characteristics of venetoclax-treated patients with pneumonia

Patients who developed pneumonia during venetoclax-based treatment were more likely to have COPD or asthma compared to patients without pneumonia (17% vs. 5%, $p = 0.001$). Patients with pneumonia compared to those without pneumonia had more comorbidities, with a median CIRS score of 6 versus 4 ($p = 0.04$). Patients who developed pneumonia were characterized by a larger tumor mass indirectly expressed by an increased median diameter of the largest lymph node (4 cm vs. 3.3 cm, $p = 0.04$), and a higher incidence of splenomegaly (71% vs. 58%, $p = 0.06$). Patients with pneumonia were more frequently diagnosed with COVID-19 compared to patients without pneumonia (35% vs. 4%, $p < 0.001$). All results are presented in Supporting Information Table 1.

3.2.1 | Prognostic factors for event-free survival in all CLL patients treated with venetoclax-based regimens

In univariate analysis, COPD/asthma, splenomegaly, anemia, and elevated levels of creatinine were associated with event occurrence (pneumonia or death, whichever occurred first; HR = 3.19, 95% CI, 1.71–5.94, $p < 0.001$; HR 2.11, 95% CI, 1.2–3.72, p = 0.01; HR 4.18, 95% CI, 2.45–7.12, $p < 0.001$; HR 3.11, 95% CI, 1.44–6.69, $p = 0.004$, respectively). There was no association between neutropenia and IgG levels with pneumonia (Table 2).

In multivariate analysis, aforementioned factors (COPD/asthma, splenomegaly, anemia, and elevated levels of creatinine) were confirmed as significant risk factors for EFS (HR = 2.08, 95% CI, 1.16–3.74, $p = 0.014$; HR 1.73, 95% CI, 1.08–2.78, $p = 0.02$; HR 3.58, 95% CI, 2.18–5.89, $p < 0.001$; HR 2.13, 95% CI, 1.10–4.11, $p = 0.03$, respectively; Table 3).

3.2.2 | Prognostic factors for event-free survival in CLL patients treated with the R-VEN regimen

In univariate analysis, male sex, splenomegaly, anemia, and elevated levels of creatinine were risk factors for event occurrence (pneumonia or death; HR 1.92, 95% CI, 1.02–3.61, $p = 0.044$; HR 2.03, 95% CI, 1.03–4.0, $p = 0.042$; HR 4.16, 95% CI, 2.22–7.8, $p < 0.001$; HR 4.08, 95% CI, 1.56–10.7, $p = 0.004$, respectively; Table 4).

In multivariate model, male sex, anemia, and elevated levels of creatinine remained risk factors for EFS (HR 1.91, 95% CI, 1.09–3.33, $p = 0.02$; HR 4.48, 95% CI, 2.49–8.07, $p < 0.001$; HR 2.79, 95% CI, 1.24–6.3, $p = 0.01$, respectively; Table 5).

3.3 | Overall survival

The occurrence of pneumonia in CLL patients treated with venetoclax-based regimens was associated with inferior OS ($p < 0.001$; Figure 1). OS analyses were also performed within two studied cohorts of patients (treated with the R-VEN and O-VEN regimen). Patients with R/R CLL treated with the R-VEN regimen, who developed pneumonia, had a worse OS ($p < 0.001$), whereas in a cohort of CLL patients treated with the O-VEN regimen, as a first-line therapy, the occurrence of pneumonia had no impact on OS ($p = 0.45$; Figures 2 and 3).

TABLE 2 Univariate analyses of event-free survival (EFS) in chronic lymphocytic leukemia (CLL) patients treated with venetoclax-based regimens.

Risk factor	Category	HR	95% CI	*p* value	OR	95% CI	*p* value
Sex	Female	0.76	(0.47–1.25)	0.28	0.81	(0.48–1.34)	0.41
Hypertension	Yes	1.04	(0.65–1.65)	0.88	1.07	(0.65–1.74)	0.80
Chronic obstructive pulmonary disease (COPD)/asthma	Yes	3.19	(1.71–5.94)	<0.001	4.3	(1.78–10.37)	0.001
Coronary artery disease/stable heart failure	Yes	1.41	(0.76–2.63)	0.27	1.37	(0.69–2.71)	0.37
Chronic kidney disease	Yes	1.46	(0.70–3.05)	0.32	1.32	(0.59–2.97)	0.50
CIRS	>6	1.38	(0.86–2.22)	0.18	1.58	(0.96–2.6)	0.07
Splenomegaly	Yes	2.11	(1.2–3.72)	0.01	2.12	(1.22–3.68)	0.007
B symptoms	Yes	1.32	(0.76–2.31)	0.33	1.22	(0.7–2.13)	0.48
Neutropenia (Absolute Neutrophil Count, ANC < 1.0 G/L)	Yes	1.04	(0.64-1.69)	0.87	1.51	(0.9-2.52)	0.11
Anemia (Hb < 8 g/dL)	Yes	4.18	(2.45–7.12)	<0.001	4.02	(2.0–8.02)	<0.001
EASIX score	No	0.99	(0.94–1.04)	0.72	0.97	(0.91–1.02)	0.23
Creatinine (mg/dL)	No	3.11	(1.44–6.69)	0.004	2.62	(1.05–6.57)	0.039
Hemoglobin (g/L)	No	0.87	(0.79–0.96)	0.008	0.9	(0.81–1.01)	0.058
White blood cells (G/L)	No	1.0	(1.0–1.0)	0.07	–	—	—
Platelets (G/L)	No	1.0	(1.0–1.0)	0.90	–	—	—
LDH (U/L)	No	1.0	(1.0–1.0)	0.86	–	—	—
Lymphocytes CD4/CD8 ratio	No	1.17	(0.84–1.64)	0.35	1.26	(0.81–1.97)	0.30
β2-Microglobulin (mg/L)	No	1.01	(0.89–1.15)	0.88	1.03	(0.89–1.19)	0.65
Immunoglobulin IgG (g/L)	No	0.93	(0.83–1.04)	0.19	0.94	(0.84–1.01)	0.23

Abbreviations: CI, confidence interval; CIRS, Cumulative Illness Rating Scale; EASIX, Endothelial Activation and Stress Index; HR, hazard ratio; LDH, lactate dehydrogenase; OR, odds ratio.

TABLE 3 Multivariate analyses of event-free survival (EFS) in chronic lymphocytic leukemia (CLL) patients treated with venetoclax-based regimens.

Risk factor	Category	HR	95% CI	*p* value
Chronic obstructive pulmonary disease (COPD)/asthma	Yes	2.08	(1.16–3.74)	0.014
Splenomegaly	Yes	1.73	(1.08–2.78)	0.02
Anemia (Hb < 8 g/dL)	Yes	3.58	(2.18–5.89)	<0.001
Creatinine (mg/dL)	No	2.13	(1.10–4.11)	0.03

Cox regression model, $\chi^2 = 39.68$; df = 4; $p < 0.001$.
Abbreviations: CI, confidence interval; HR, hazard ratio.

4 | DISCUSSION

Here, we present one of the largest real-world studies assessing the incidence and risk factors for pneumonia as one of the most serious and probably underestimated complications of treatment in patients with CLL treated with venetoclax-based regimens.

We showed that pneumonia is an unfavorable prognostic factor for OS in CLL patients treated with venetoclax-based regimens, especially in patients with R/R CLL treated with venetoclax in combination with rituximab. We found significantly higher rates of pneumonia in the entire cohort of CLL patients compared to the registration trials (the CLL-14 and the MURANO trial) [4, 5]. This may be due to, on the one hand, the fact that most of the data were collected during the SARS-CoV-2 pandemic, and on the other hand, that pneumonia was more common in the cohort of R/R CLL patients who were intensively pretreated and had adverse clinical features.

In the MURANO trial, the incidence of pneumonia of any grade in R/R CLL patients treated with venetoclax plus rituximab was 9.3%, the most frequent type of infection [4].

Among CLL patients treated with venetoclax in the first line of the CLL-14 trial the incidence of pneumonia, which, as in the MURANO trial, was the most common type of infection at grade ≥3, was 4.7% [5].

However, in a real-world study of the clinical efficacy and tolerability of venetoclax in combination with rituximab in patients with R/R CLL, the incidence of pneumonia was 23.9%, higher than in the MURANO registration trial [6].

TABLE 4 Univariate analyses of event-free survival (EFS) in chronic lymphocytic leukemia (CLL) patients treated with rituximab plus venetoclax (R-VEN) regimen.

Risk factor	Category	HR	95% CI	*p* value	OR	95% CI	*p* value
Sex	Female Male	0.52 1.92	(0.28–0.98) (1.02–3.61)	0.044	0.55 1.8	(0.28–0.98) (0.3–1.04)	0.064
Hypertension	Yes	0.93	(0.53–1.62)	0.8	1.01	(0.55–1.86)	0.963
Chronic obstructive pulmonary disease (COPD)/asthma	Yes	2.09	(0.89–4.91)	0.092	1.66	(0.55–5.03)	0.366
Coronary artery disease/stable heart failure	Yes	1.25	(0.56–2.78)	0.583	1.33	(0.55–3.23)	0.531
Chronic kidney disease	Yes	1.5	(0.6–3.8)	0.387	1.55	(0.56–4.31)	0.394
CIRS	>6	1.57	(0.89–2.76)	0.119	1.88	(1.02–3.49)	0.043
Splenomegaly	Yes	2.03	(1.03–4.0)	0.042	2.08	(1.07–4.06)	0.031
B symptoms	Yes	1.13	(0.61–2.11)	0.690	1.1	(0.58–2.07)	0.767
Neutropenia (Absolute neutrophil count, ANC < 1.0 G/L)	Yes	1.03	(0.56–1.89)	0.923	1.35	(0.71–2.57)	0.364
Anemia (Hb < 8 g/dL)	Yes	4.16	(2.22–7.8)	<0.001	3.36	(1.53–7.38)	0.002
EASIX score		0.99	(0.93–1.06)	0.781	0.95	(0.88–1.03)	0.248
Creatinine (mg/dL)		4.08	(1.56–10.7)	0.004	2.77	(0.9–8.53)	0.073
Hemoglobin (g/L)		0.88	(0.78–0.98)	0.026	0.92	(0.81–1.04)	0.174
White blood cells (G/L)		1.0	(1.0–1.0)	0.153	–	—	—
Platelets (G/L)		1.0	(1.0–1.01)	0.433	–	—	—
LDH (U/L)		1.0	(1.0–1.0)	0.725	–	—	—
Lymphocytes CD4/CD8 ratio		1.07	(0.58–1.98)	0.818	1.09	(0.54–2.22)	0.795
β2-Microglobulin (mg/L)		0.99	(0.83–1.19)	0.955	0.99	(0.81–1.21)	0.9
Immunoglobulin IgG (g/L)		0.90	(0.77–1.04)	0.148	0.91	(0.79–1.05)	0.192

Abbreviations: CI, confidence interval; CIRS, Cumulative Illness Rating Scale (CIRS); EASIX, Endothelial Activation and Stress Index; HR, hazard ratio; LDH, lactate dehydrogenase; OR, odds ratio.

TABLE 5 Multivariate analyses of event-free survival (EFS) in chronic lymphocytic leukemia (CLL) patients treated with rituximab plus venetoclax (R-VEN) regimen.

Risk factor	Category	HR	95% CI	*p* value
Male sex	Yes	1.91	(1.09–3.33)	0.02
Anemia (Hb < 8 g/dL)	Yes	4.48	(2.49–8.07)	<0.001
Creatinine (mg/dL)	No	2.79	(1.24–6.30)	0.01

Cox regression model, $\chi^2 = 27{,}8$; df = 3; $p < 0.001$.
Abbreviations: CI, confidence interval; HR, hazard ratio.

The issue of infectious complications in CLL patients treated with venetoclax was analyzed in a real-world study conducted by the Italian Sorveglianza Epidemiologica Infezioni Fungine nelle Emopatie Maligne (SEIFEM) group [7]. This study showed the respiratory tract as the most common involved site of infections, and singled out three specific variables (COPD, previous infections, and previous treatments) as risk factors for infections in CLL patients treated with venetoclax [7].

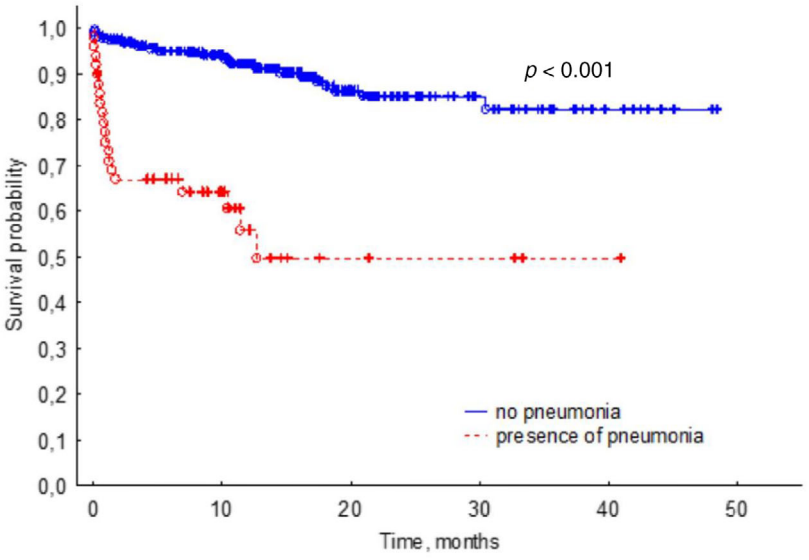
In our study, we confirmed respiratory tract infections as the most common infectious complication in CLL patients treated with venetoclax-based regimens.

We showed the occurrence of pneumonia in 20% of all CLL patients treated with venetoclax-based regimens. The incidence of pneumonia was clinically higher among patients treated with R-VEN compared to O-VEN, but without statistical significance. The viral etiology of pneumonia was clinically higher in patients treated with R-VEN.

These results differ from registration studies, which is obvious given the lack of selection of patients starting treatment in real-world settings. In our study, patients were generally older, with more comorbidities, and treated with more prior lines, reflecting the inclusion criteria for treatment with O-VEN and R-VEN regimens under the Ministry of Health program in Poland. In addition, the coincidence of SARS-CoV-2 pandemic may have had an important influence on the high number of pneumonia observed in the study. Viral pneumonia was observed in the majority of all reported pneumonia (59%). According to ESMO and NCCN guidelines, antibiotic and antifungal prophylaxis is not recommended during venetoclax treatment. All included patients received antiviral prophylaxis (acyclovir), mainly due to combination treatment with monoclonal antibodies (rituximab or obinutuzumab).

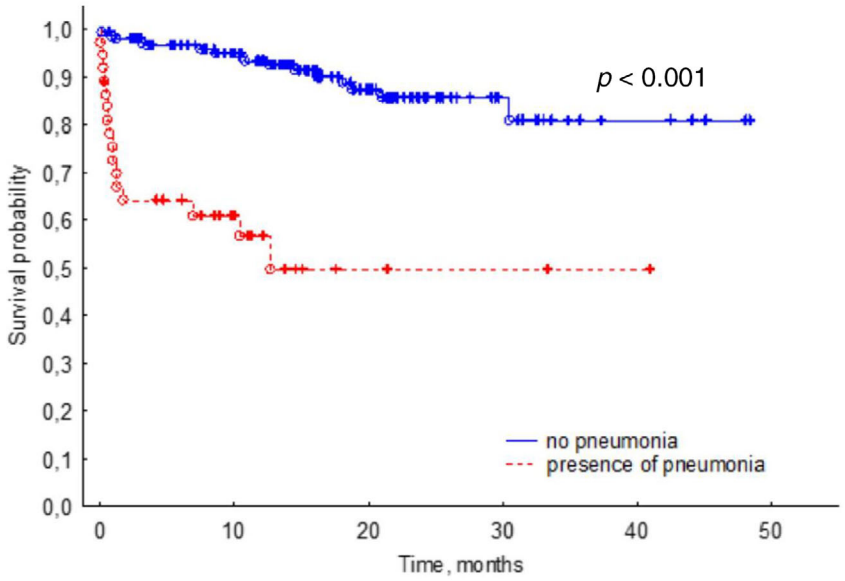
The higher incidence of pneumonia in patients treated with R-VEN may be due to more advanced disease in patients with R/R CLL, treatment-related cumulative immunosuppression (longer drug-induced B-cell depletion, T cell immunodeficiency due to previous treatment), and immunosuppression due to progressive disease manifested mainly by reduced IgG and IgA levels [8].

Focusing on the potential predictors of pneumonia during venetoclax treatment, we found that the presence of COPD or asthma,



Number at risk					
no pneumonia	205	124	53.5	20.5	4.5
presence of pneumonia	42.5	13	3.5	2	0.5

FIGURE 1 Kaplan–Meier survival curves for overall survival (OS) in all chronic lymphocytic leukemia (CLL) patients treated with venetoclax-based regimens according to occurrence of pneumonia. Median OS for patients without pneumonia was not reached. Median OS for patients with pneumonia was 12.6 (1.0–NA) months. Log-rank test $p < 0.001$.



Number at risk					
no pneumonia	135	89.5	38	12	2.5
presence of pneumonia	33	10	2.5	1.5	0.5

FIGURE 2 Kaplan–Meier survival curves for overall survival (OS) in chronic lymphocytic leukemia (CLL) patients treated with rituximab plus venetoclax (R-VEN) regimen according to occurrence of pneumonia. Median OS for CLL patients without pneumonia treated with R-VEN regimen was not reached. Median OS for CLL patients with pneumonia treated with R-VEN regimen was 12.5 (0.9–NA) months. Log-rank test $p < 0.001$.

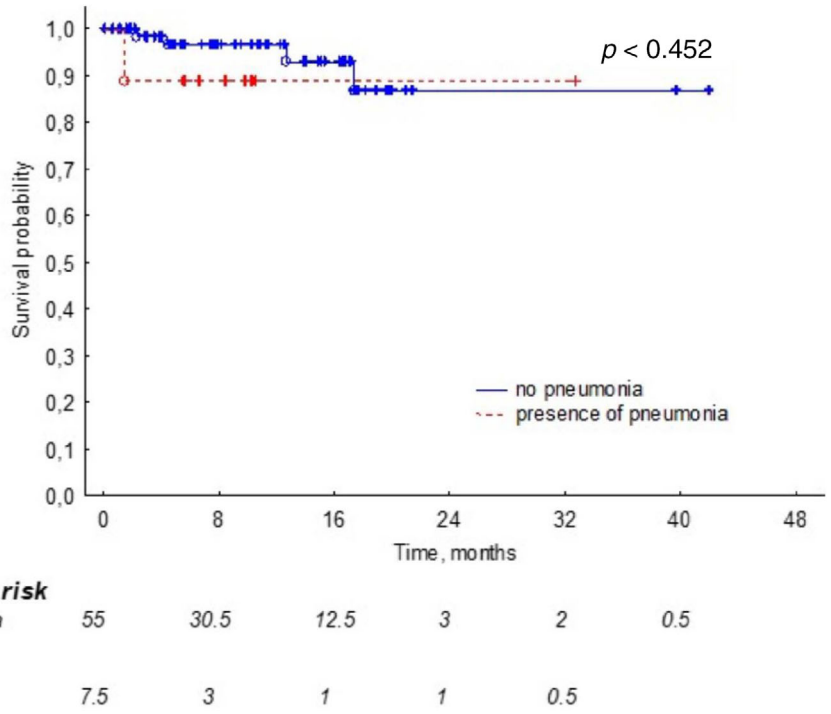


FIGURE 3 Kaplan–Meier survival curves for overall survival (OS) in chronic lymphocytic leukemia (CLL) patients treated with obinutuzumab plus venetoclax (O-VEN) regimen according to occurrence of pneumonia. Median OS for CLL patients treated with O-VEN: not reached. Log-rank test $p < 0.001$.

splenomegaly, increased levels of creatinine at baseline, and anemia were the most predictive of pneumonia in all CLL patients.

In the most vulnerable R/R CLL patients treated with R-VEN, the key predictors of pneumonia were anemia and elevated creatinine levels.

Previous studies emphasized the significance of impaired renal function as a negative prognostic factor in patients with CLL [9]. In acquired pneumonia, renal insufficiency manifested by elevated blood urea nitrogen levels was associated with increased mortality in CLL patients [10].

We suggest that in the era of new targeted therapies, an increase in creatinine levels remains a significant negative prognostic factor. Our study showed that an increase in serum creatinine that does not meet the definition of acute renal failure can serve as a sensitive predictor of pneumonia during venetoclax treatment.

Splenomegaly is another risk factor for pneumonia observed in our study. In patients with more active disease expressed by the presence of an enlarged spleen, defenses against infectious agents may be weakened, increasing the risk of developing pneumonia during treatment. Previous data confirmed the potential associations between splenomegaly and severity of lung involvement in COVID-19 patients [11].

The presence of COPD is considered as a risk factor for pneumonia [12, 13]. We showed that underlying COPD/asthma is associated with pneumonia during treatment with venetoclax-based regimens. Our results are consistent with previously published real-world data from CLL patients treated with venetoclax, which identified COPD as a risk factor for severe infections [7, 14].

A significant predictor of pneumonia in the entire cohort of CLL patients treated with venetoclax was severe anemia defined as hemoglobin below 8 g/dL. Anemia is a well-recognized adverse factor in patients with acquired pneumonia, and when severe, is independently associated with mortality [15]. Recently, the importance of the negative role of anemia has been emphasized in viral infections, including viral pneumonia. It has been shown that the presence of anemia was associated with disease progression and mortality in patients with both COVID-19 [16–18] and non-COVID-19-related pneumonia [14, 19]. Therefore, given our results, it seems that hemoglobin level may be a simple, easily modifiable factor in predicting the risk of lung infection. The results of our study suggest that hemoglobin levels should be closely monitored in patients receiving venetoclax-based treatment, and perhaps normalizing hemoglobin levels may be the key to improving treatment outcomes.

Interestingly, we showed no association between the presence of neutropenia during treatment and pulmonary infections, suggesting that the most common complication of venetoclax treatment remains insignificant in terms of increasing the risk of infections.

Finally, our study showed that CLL patients treated with venetoclax-based regimens who developed pneumonia had worse OS than patients without pneumonia. This finding was particularly significant in a cohort of patients with R/R CLL treated with R-VEN regimen. The lack of differences in OS between patients with and without pneumonia in the cohort of patients treated with O-VEN may be due to the first-line treatment and lower cumulative toxicity of previous therapies.

There were some limitations in our study. First, due to the retrospective nature of the study, complete data on all dates of pneumonia and the detailed microbiological etiology and antibiotic prophylaxis used were lacking. Second, we had limited data on vaccination history against SARS-CoV-2 and immune response, so this information as a potential confounding factor could not be included in the analysis.

5 | CONCLUSIONS

In real-world settings, patients with CLL treated with venetoclax-based regimens are at a higher risk of pneumonia, especially patients with R/R CLL treated with venetoclax in combination with rituximab compared to registration trials.

Pneumonia has a negative impact on OS in patients with CLL receiving venetoclax-based therapy. In patients treated with first-line venetoclax and obinutuzumab, despite the high burden of comorbidities, the occurrence of pneumonia does not affect OS.

The presence of COPD/asthma, splenomegaly, severe anemia, and elevated creatinine levels are the key predictors/risk factors of pneumonia during treatment with venetoclax-based regimens and identify a subgroup of patients at high risk of pneumonia who particularly require anti-infective prophylaxis, appropriate treatment of underlying conditions, and close monitoring. Neutropenia, as the most common hematological complication during venetoclax treatment, is not a risk factor for pneumonia.

In conclusion, our real-world study highlighted the important issue of pneumonia and its impact on OS in the CLL patient population treated with venetoclax-based regimens, especially in patients following earlier lines of treatment, with R/R disease.

AUTHOR CONTRIBUTIONS

Conceptualization: Elżbieta Kalicińska. *Methodology*: Elżbieta Kalicińska; Iga Andrasiak; Anna Skotny; and Joanna Drozd-Sokolowska. *Validation*: Elżbieta Kalicińska and Tomasz Wrobel. *Formal analysis*: Elżbieta Kalicińska; Iga Andrasiak; and Anna Skotny. *Investigation*: Elżbieta Kalicińska and Paula Jablonowska-Babij. *Resources*: Paula Jablonowska-Babij; Marta Morawska; Elżbieta Iskierka-Jażdżewska; Joanna Drozd-Sokolowska; Ewa Paszkiewicz-Kozik; Łukasz Szukalski; Judyta Strzała; Urszula Gosik; and Jakub Dębski. *Data curation*: Elżbieta Kalicińska; Iga Andrasiak; and Paula Jablonowska-Babij. *Writing—original draft preparation*: Elżbieta Kalicińska. *Writing—editing and review*: Joanna Drozd-Sokolowska; Krzysztof Jamroziak; and Tomasz Wrobel. *Visualization*: Elżbieta Kalicińska and Paula Jablonowska-Babij. *Supervision*: Krzysztof Jamroziak and Tomasz Wrobel. All the authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

ETHICS STATEMENT

This study was performed in accordance with the Wroclaw Medical University ethics committee.

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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