Serious Infections in Patients With CLL/SLL Treated With Combination Venetoclax and Obinutuzumab Compared With Those Treated With Zanubrutinib: A Real-World Study

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CONCLUSIONS

- Patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) treated with venetoclax + obinutuzumab had a significantly higher risk of serious infections and an increased usage of intravenous immunoglobulin (IVIG) and granulocyte colony-stimulating factor (GCSF) administration and hospitalization compared with those treated with zanubrutinib
- Patients treated with venetoclax + obinutuzumab were more likely to receive IVIG and GCSF treatment than those treated with zanubrutinib; however, they were at higher risk of serious infections even with prophylactic IVIG/GCSF treatment
- Patients treated with zanubrutinib had a similar rate of serious infections compared with untreated patients with CLL/SLL, with both cohorts showing lower event rates than the venetoclax + obinutuzumab cohorts
- In patients with a higher risk of infections, zanubrutinib could be considered as a treatment option in lieu of venetoclax + obinutuzumab

INTRODUCTION

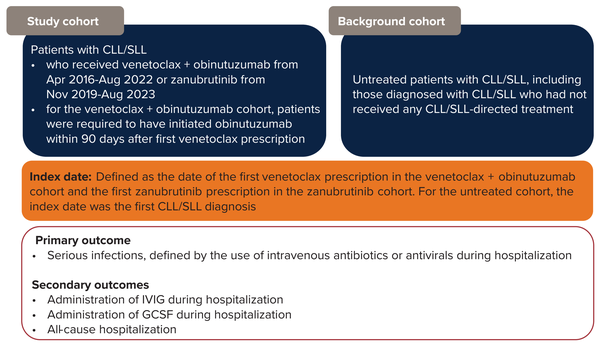
- As serious infections can lead to severe complications,[1] it is critical to consider their risk in treatment decisions, especially for patients with cancer who have compromised immune systems
- The association between CLL/SLL-directed therapies and serious infection risks remains a significant concern, prompting the need for treatments with lower risks[2]
- This real-world study described and compared the rates of serious infections at 18, 24, and 36 months following the initiation of venetoclax + obinutuzumab and zanubrutinib in patients with CLL/SLL

METHODS

Data Source

- This retrospective cohort study (**Figure 1**) used the Symphony Health Solutions Database, which contains deidentified and tokenized information that allows linkage of patient-level data from various sources, such as hospital claims, physician offices, and prescription data, with record dates as recent as 1 month prior

Figure 1. Design, Patient Cohorts and Main Outcome Measures



Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; GCSF, granulocyte colony-stimulating factor; IVIG, intravenous immunoglobulin.

Statistical Analysis

- Proportions and event rates of serious infections were evaluated at 18-, 24-, and 36-months of follow-up in venetoclax + obinutuzumab and zanubrutinib cohorts. The proportions and event rates of IVIG and GCSF administration and hospitalization were evaluated at 24-month follow-up. In addition, hospitalization was evaluated at 36-month follow-up
- A Cox proportional hazards model was used to calculate the hazard ratios (HRs) of serious infections, IVIG and GCSF administration, and hospitalization between venetoclax + obinutuzumab and zanubrutinib cohorts
- Inverse probability of treatment weighting (IPTW) was used to balance baseline confounders (age, sex, race and ethnicity, Charlson Comorbidity Index, and region) between the two cohorts
- Additionally, the event rate of serious infections in the untreated cohort at 18- and 24-month follow-up was calculated for comparison with the two study cohorts

RESULTS

Baseline Characteristics

- A total of 2104 patients with CLL/SLL received venetoclax + obinutuzumab, and 2650 patients received zanubrutinib. The untreated CLL/SLL cohort included 145,390 patients
- Patients receiving zanubrutinib were older than those treated with venetoclax + obinutuzumab (median age, 73 vs 68 years) (**Table 1**), and the proportion of female patients in the zanubrutinib cohort was higher than that in the venetoclax + obinutuzumab cohort (40% vs 35%)

Serious Infections

- At 18-month follow-up, the proportions and risks of serious infections were higher in the venetoclax + obinutuzumab cohort vs the zanubrutinib cohort (10.1% vs 5.8%; IPTW-weighted HR, 1.60; 95% CI, 1.28-1.98). A similar trend was observed at 24-month follow-up (12.0% vs 6.8%; IPTW-weighted HR, 1.53; 95% CI, 1.25-1.87). The same trend was observed at 36-month follow-up (**Table 2**)
- Cumulative incidence function curves demonstrated a consistently higher rate of serious infections in the venetoclax + obinutuzumab cohort vs the zanubrutinib cohort, with the difference widening over time (**Figures 2a**)

IVIG and GCSF Administration

- During 24-month follow-up, the venetoclax + obinutuzumab cohort also showed a higher usage of IVIG and GCSF administration than the zanubrutinib cohort (IVIG administration: IPTW-weighted HR, 1.93, 95% CI, 1.46-2.56; GCSF administration: IPTW-weighted HR, 3.75, 95% CI, 2.72-5.18), aligning with the cumulative incidence function curves (**Table 2**, **Figures 2b-2c**)

Hospitalization

- During 24-month follow-up, the venetoclax + obinutuzumab cohort also showed a higher rate of hospitalization than the zanubrutinib cohort (IPTW-weighted HR, 1.32, 95% CI, 1.20-1.46), aligning with the cumulative incidence function curves (**Table 2**). A similar trend was observed at 36-month follow-up (46.7% vs 33.0%; IPTW weighted HR, 1.32; 95% CI, 1.20-1.45) (**Figure 2d**)

Serious Infections Compared With Untreated Patients

- Compared with untreated patients, zanubrutinib-treated patients had a similar event rate of serious infections at 24 months of follow-up (untreated CLL/SLL: 0.39 per 100 person-months; 95% CI, 0.38-0.40; zanubrutinib: 0.37; 95% CI, 0.32-0.43). Both cohorts experienced lower event rates than the venetoclax + obinutuzumab cohort (0.59; 95% CI, 0.52-0.67) (**Table 3**)

Table 1. Demographics and Baseline Characteristics at Treatment Initiation

	Venetoclax + obinutuzumab (n=2104)	Zanubrutinib (n=2650)
Age at index date, years		
Mean (SD)	66 (9.2)	70 (8.1)
Median	68	73
Sex, n (%)		
Female	735 (34.9)	1069 (40.3)
Male	1369 (65.1)	1581 (59.7)
Race and ethnicity, n (%)		
White, non-Hispanic	1422 (84.4)	1759 (83.7)
Black, non-Hispanic	160 (9.5)	187 (8.9)
Asian, non-Hispanic	14 (0.8)	39 (1.9)
Hispanic	81 (4.8)	108 (5.1)
Charlson Comorbidity Index, n (%)		
0	920 (43.7)	1151 (43.4)
1	366 (17.4)	459 (17.3)
2	328 (15.6)	401 (15.1)
3	188 (8.9)	230 (8.7)
≥4	302 (14.4)	409 (15.4)

Table 2. Serious Infections, IVIG and GCSF Administration, and Hospitalization During Different Follow-Up Periods

	Venetoclax + obinutuzumab (n=2104)	Zanubrutinib (n=2650)
Overall serious infections		
18-month follow-up		
n (%)	212 (10.1)	155 (5.8)
Event rate (per 100 patient-months) (95% CI)	0.64 (0.55-0.73)	0.37 (0.32-0.44)
IPTW-weighted HR (95% CI)	1.60 (1.28-1.98)	Reference
24-month follow-up		
n (%)	253 (12.0)	179 (6.8)
Event rate (per 100 patient) months (95% CI)	0.59 (0.52-0.67)	0.37 (0.32-0.43)
IPTW-weighted HR (95% CI)	1.53 (1.25-1.87)	Reference
36-month follow-up		
n (%)	309 (14.7)	187 (7.1)
Event rate (per 100 patient) months (95% CI)	0.53 (0.47-0.59)	0.35 (0.30-0.40)
IPTW-weighted HR (95% CI)	1.56 (1.28-1.89)	Reference
IVIG administration at 24-month follow-up		
n (%)	138 (6.6)	90 (3.4)
Event rate (per 100 patient) months (95% CI)	0.31 (0.27-0.37)	0.18 (0.15-0.23)
IPTW-weighted HR (95% CI)	1.93 (1.46-2.56)	Reference
GCSF administration at 24-month follow-up		
n (%)	160 (7.6)	54 (2.0)
Event rate (per 100 patient) months (95% CI)	0.37 (0.32-0.43)	0.11 (0.08-0.14)
IPTW-weighted HR (95% CI)	3.75 (2.72-5.18)	Reference
Hospitalization		
24-month follow-up		
n (%)	850 (40.4)	834 (31.5)
Event rate (per 100 patient) months (95% CI)	2.42 (2.26-2.59)	1.98 (1.85-2.12)
IPTW-weighted HR (95% CI)	1.32 (1.20-1.46)	Reference
36-month follow-up		
n (%)	982 (46.7)	874 (33.0)
Event rate (per 100 patient) months (95% CI)	2.11 (1.98-2.24)	1.90 (1.77-2.03)
IPTW-weighted HR (95% CI)	1.32 (1.20-1.45)	Reference

P-values for all HRs are <.0001.
Abbreviations: GCSF, granulocyte colony-stimulating factor; HR, hazard ratio; IPTW, Inverse probability of treatment weighting; IVIG, intravenous immunoglobulin.

Table 3. Event Rates of Serious Infections in Venetoclax + Obinutuzumab, Zanubrutinib, and Untreated Cohorts

	18 Months		24 Months	
	n (%)	Rate (95% CI)[a]	n (%)	Rate (95% CI)[a]
Study cohort 1: venetoclax + obinutuzumab	212 (10.1)	0.64 (0.55-0.73)	253 (12.0)	0.59 (0.52-0.67)
Study cohort 2: zanubrutinib	155 (5.8)	0.37 (0.32-0.44)	179 (6.8)	0.37 (0.32-0.43)
Background cohort: untreated patients with CLL/SLL	11,371 (7.8)	0.46 (0.45-0.47)	12,821 (8.8)	0.39 (0.38-0.40)

[a]Per 100 patient-months.
Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma.

Figure 2. Cumulative Incidence Curve of (a) Serious Infections, (b) IVIG and (c) GCSF Administration, and (d) Hospitalization in Venetoclax + Obinutuzumab and Zanubrutinib Cohorts

Abbreviations: GCSF, granulocyte colony-stimulating factor; IVIG, intravenous immunoglobulin.

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