Real-world treatment patterns, reasons for discontinuation, and survival outcomes among patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) receiving second or later lines of therapy in a contemporary population treated in the United States

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Introduction

- Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in the United States, accounting for over 21,000 diagnoses in 2020[1]
- Some patients with CLL/SLL do not require the initiation of first-line (1L) therapy due to the indolent nature of their disease
- Other patients, however, experience significant disease progression following 1L treatment and require additional therapeutic options to treat relapsed/refractory (R/R) disease
- The development of targeted agents, such as ibrutinib and venetoclax, has transformed the CLL/SLL treatment paradigm both in the 1L setting and for previously treated patients, and there is not a clear standard of care for CLL/SLL in later lines of therapy (LOTs)
- This study examines the characteristics, treatment patterns, and outcomes of a large cohort of real-world patients receiving 2 or more LOTs

Methods

- Patients meeting the following criteria were identified from the COTA real-world database:
  - Inclusion:
    - Aged ≥ 18 years at diagnosis with a confirmed CLL/SLL diagnosis
    - Initiated 2L therapy between January 1, 2014 and June 30, 2021
  - Exclusion:
    - Documented diagnosis of a concurrent primary malignancy or transformation at the time of CLL/SLL diagnosis
    - History of other primary malignancies, excluding benign skin cancers, within 3 years prior to CLL/SLL diagnosis
- COTA's database is a Health Insurance Portability and Accountability Act (HIPAA)-compliant real-world database comprised of longitudinal data pertaining to the diagnosis, clinical management, and outcomes of patients with cancer
- Data were abstracted from the electronic health records (EHRs) of partnered academic and community health care provider sites in the United States with a primary geographic concentration in the Eastern and Southern regions of the United States
- The index date for the study was the date of initiation of 2L therapy and was updated to the start of each subsequent LOT for LOT-specific analyses
- Patient and clinical characteristics and treatment patterns were summarized as appropriate using means, medians, and/or patient counts and percentages
- Time to event outcomes, including real-world progression-free survival (rwPFS) and real-world overall survival (rwOS), were assessed for the study population and by LOT using the Kaplan-Meier method

Results

Characteristics

- A real-world population of 1102 eligible patients with the following characteristics were included in the study (**Table 1**):
  - Median age at diagnosis of 64 years [IQR: 57, 72]
  - Median age at 2L initiation of 70 years [IQR: 63, 78]
  - Male (60.9%)
  - White (83.0%)
  - Treated in the community setting (88.1%)
- Patients were most commonly diagnosed in 2014 or earlier (74.1%) (**Table 1**)
- Among patients with test results for the given molecular marker, marker positivity included: 59% (N=314/536) del(13q), 35% (N=135/385) del(11q), 23.1% (N=86/372) del(17p), 20.6% (N=102/496) TP53 mutation, and 32.3% (N=70/217) IGHV mutated

Table 1. Patient and clinical characteristics by line of therapy

Characteristics	2L (N=1102)	3L (N=468)	4L (N=201)	5L (N=75)	6L (N=25)
Age at initiation of LOT, n (%)					
< 65 years	560 (50.8)	126 (26.9)	52 (25.9)	24 (32.0)	6 (4.0)
≥ 65 years	542 (49.2)	342 (73.1)	149 (74.1)	51 (68.0)	19 (76.0)
Age at initiation of LOT, median [IQR]	70.00 [63.00, 78.00]	71.00 [64.00, 79.00]	72.00 [64.00, 79.00]	70.00 [64.00, 78.50]	74.00 [69.00, 82.00]
Sex, n (%)					
Female	431 (39.1)	192 (41.0)	77 (38.3)	22 (29.3)	4 (16.0)
Race, n (%)					
Black or African American	84 (7.6)	43 (9.2)	22 (10.9)	8 (10.7)	3 (12.0)
Asian	10 (0.9)	5 (1.1)	2 (1.0)	1 (1.3)	0 (0.0)
Other Race	70 (6.4)	35 (7.5)	15 (7.5)	6 (8.0)	1 (4.0)
White	915 (83.0)	369 (78.8)	158 (78.6)	59 (78.7)	20 (80.0)
Unknown	23 (2.1)	16 (3.4)	4 (2.0)	1 (1.3)	1 (4.0)
Ethnicity, n (%)					
Hispanic	96 (8.7)	38 (8.1)	19 (9.5)	8 (10.7)	3 (12.0)
Non-Hispanic	954 (86.6)	406 (86.8)	172 (85.6)	65 (86.7)	21 (84.0)
Unknown	52 (4.7)	24 (5.1)	10 (5.0)	2 (2.7)	1 (4.0)
Practice type, n (%)					
Academic	131 (11.9)	66 (14.1)	32 (15.9)	11 (14.7)	3 (12.0)
Community	971 (88.1)	402 (85.9)	169 (84.1)	64 (85.3)	22 (88.0)
Year of initial diagnosis					
≤2014	817 (74.1)	368 (78.6)	168 (83.6)	61 (81.3)	22 (88.0)
2015-2019	275 (25.0)	98 (20.9)	32 (15.9)	14 (18.7)	3 (12.0)
2020+	10 (0.9)	2 (0.4)	1 (0.5)	0 (0.0)	0 (0.0)
Follow-up time from initial diagnosis (months), median [IQR]	101.46 [67.06, 142.33]	112.31 [78.26, 153.20]	118.32 [82.92, 154.65]	121.25 [85.50, 154.75]	132.30 [88.47, 152.42]
Time from initial diagnosis to R/R (months), median [IQR]	61.48 [33.07, 99.86]	59.18 [31.36, 100.05]	57.50 [33.73, 94.98]	50.50 [30.28, 92.43]	50.04 [37.71, 76.73]
Follow-up time from R/R (months), median [IQR]	35.05 [18.45, 56.61]	48.10 [31.22, 65.55]	53.39 [39.16, 74.27]	63.72 [48.35, 79.99]	69.37 [63.72, 83.41]
ECOG status, n (%)					
0-1	753 (68.3)	291 (62.2)	122 (60.7)	44 (58.7)	12 (48.0)
2+	42 (3.8)	19 (4.1)	6 (3.0)	4 (5.3)	1 (4.0)
Unknown	307 (27.9)	158 (33.8)	73 (36.3)	27 (36.0)	12 (48.0)
Rai stage, n (%)					
0	294 (26.7)	121 (25.9)	52 (25.9)	23 (30.7)	6 (24.0)
I	231 (21.0)	93 (19.9)	33 (16.4)	15 (20.0)	4 (16.0)
II	105 (9.5)	40 (8.5)	12 (6.0)	6 (8.0)	3 (12.0)
III/IV	190 (17.2)	84 (17.9)	41 (20.4)	12 (16.0)	3 (12.0)
Unknown	282 (25.6)	130 (27.8)	63 (31.3)	19 (25.3)	9 (36.0)
Cytogenetic risk*, n (%)					
Low risk	37 (3.4)	14 (3.0)	3 (1.5)	0 (0.0)	0 (0.0)
High risk	230 (20.9)	116 (24.8)	52 (25.9)	21 (28.0)	10 (40.0)
Unknown	835 (75.8)	338 (72.2)	146 (72.6)	54 (72.0)	15 (60.0)
Bulky disease, n (%)**					
Presence	84 (7.6)	37 (7.9)	19 (9.5)	6 (8.0)	2 (8.0)
Absence	131 (11.9)	61 (13.0)	21 (10.4)	6 (8.0)	3 (12.0)
Unknown	887 (80.5)	370 (79.1)	161 (80.1)	63 (84.0)	20 (80.0)

*High cytogenetic risk defined as at least 1 of: del (17p) and/or TP53 mutation and/or IGHV unmutated; low cytogenetic risk defined as none of: del (17p) and/or TP53 mutation and/or IGHV unmutated; and unknown defined as at least 1 unknown test result and none of: del (17p) and/or TP53 mutation and/or IGHV unmutated)
**Bulky disease is reported as documented in the EHR by the treating physician.
LOT, line of therapy; IQR, interquartile range; R/R, relapsed/refractory; ECOG, Eastern Cooperative Oncology Group.

Table 2. Reasons for 2L treatment discontinuation overall and by treatment category

	Overall (N=690)	Ibrutinib (N=243)	BR (N=191)	Acalabrutinib (N=20)	Rituximab, Venetoclax (N=33)	Chlorambucil, Obinutuzumab (N=31)	FCR (N=26)	Venetoclax (N=16)
Reason, n (%)								
Death	47 (6.8)	34 (14.0)	1 (0.5)	4 (20.0)	1 (3.0)	0 (0.0)	1 (3.8)	1 (6.2)
Progression	44 (6.4)	25 (10.3)	4 (2.1)	0 (0.0)	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)
Toxicity	200 (29.0)	115 (47.3)	37 (19.4)	8 (40.0)	5 (15.2)	3 (9.7)	6 (23.1)	3 (18.8)
Physician preference	65 (9.4)	15 (6.2)	21 (11.0)	5 (25.0)	4 (12.1)	4 (12.9)	2 (7.7)	2 (12.5)
Other	334 (48.4)	54 (22.2)	128 (67.0)	3 (15.0)	23 (69.7)	23 (74.2)	17 (65.4)	10 (62.5)

BR, Bendamustine, Rituximab; FCR, Fludarabine, Cyclophosphamide, Rituximab.

Treatment patterns

- The most common treatments among patients receiving 2L therapy were ibrutinib, bendamustine + rituximab (BR), rituximab, acalabrutinib, and investigational regimen (**Figure 1**)
- In 3L, the most common regimens were ibrutinib, acalabrutinib, and BR (**Figure 1**)
- Among patients who received 4L, common regimens included ibrutinib, rituximab + venetoclax, and acalabrutinib (**Figure 1**)
- Utilization of BTK and BCL2 inhibitors and anti-CD20 antibodies increased from 2014 (39.9%, 0.0%, and 9.2%, respectively) to 2022 (48.9%, 34.0%, and 25.5%, respectively), while utilization of chemoimmunotherapy decreased markedly over the same time period (from 37.9% to 6.4%) (**Figure 2**)

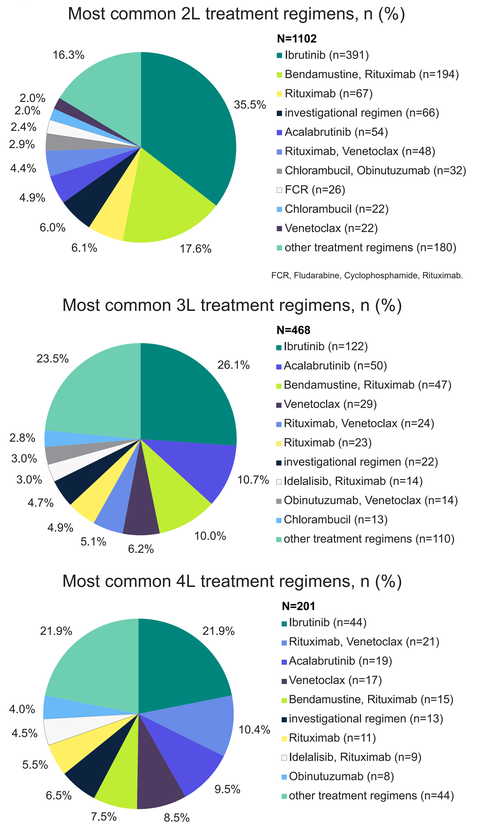
Reasons for treatment discontinuation

- Among patients who received 2L, 77.5% (N=854/1102) discontinued therapy, and 22.5% (N=248/1102) were on ongoing therapy at the end of follow-up
- Patients who received 2L BTKi therapy discontinued therapy primarily due to toxicity (47.3% [N=115/243] among patients who received ibrutinib and 40.0% [N=8/20] among patients who received acalabrutinib) or death (14.0% [N=34/243] among patients who received ibrutinib and 20.0% [N=4/20] among patients who received acalabrutinib) (**Table 2**)
- Patients who received rituximab-containing therapies often discontinued due to toxicity (19.4% [N=37/191] among patients who received BR, 15.2% [N=5/33] among patients who received rituximab + venetoclax, and 23.1% [N=6/26] among patients who received cyclophosphamide + fludarabine + rituximab [FCR]) (**Table 2**)
- CLL disease progression and physician preference were also common reasons for treatment discontinuation in 2L (**Table 2**)
- Approximately 18% of patients died after initiating 2L and prior to initiating 3L, and 25.5% of all patients died prior to initiation of 4L. About 17% of patients completed or discontinued 2L therapy and did not initiate 3L therapy (**Figure 3**)

Outcomes

- Among the study population, median rwPFS from initiation of 2L was 31.4 months (95% CI: 28.6, 35.5), and median rwOS from initiation of 2L was 79.0 months (95% CI: 68.9, 85.3) (**Figures 4, 5**)

Figure 1. Most common treatments by LOT 2-4



FCR, Fludarabine, Cyclophosphamide, Rituximab.

Figure 2. Treatment utilization 2014-2022

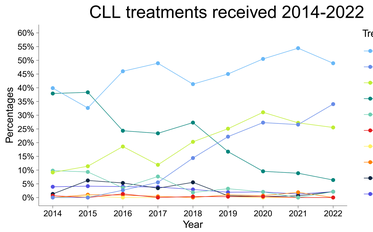


Figure 3. Sankey plot - treatment by LOT

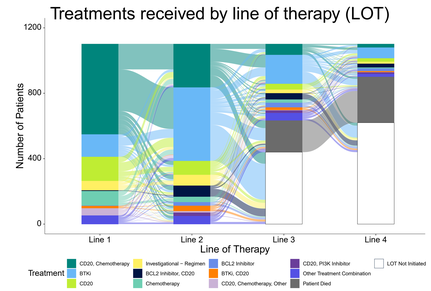


Figure 4. rwPFS from 2L initiation

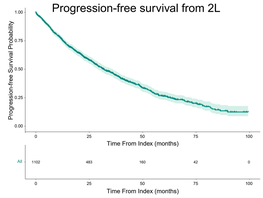
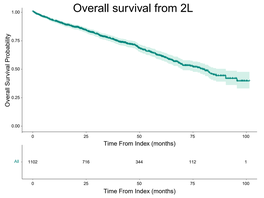


Figure 5. rwOS from 2L initiation



Conclusions

- Although targeted therapies have improved the outcomes of patients with CLL/SLL, these analyses suggest that there is still an unmet need, with a high proportion of patients discontinuing treatments due to progression or toxicity
- Furthermore, 2L+ patients continue to experience poor survival outcomes
- Innovative treatment options and novel mechanisms of action are needed to improve CLL patient outcomes

References
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