Treatment Burden Among Patients Aged 75 Years or Older With Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

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CONCLUSIONS

- Treatment burden remains substantial in elderly patients with CLL/SLL, with >50% of those aged 75-79 years and over one-third of those aged ≥80 years requiring subsequent therapy
  - However, identifying who will avoid 2L treatment remains challenging
- Treatment burden is likely underestimated, as rates of subsequent therapy are expected to increase with longer follow-up
- These findings underscore the importance of front-line choices that account for longitudinal treatment sequencing, particularly in older patients

INTRODUCTION

- Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is the most common leukemia among adults in the US, with median age at diagnosis of 70 years and median age at death of 82 years[1]
- Previous real-world studies prior to the introduction of novel therapies reported various treatment burdens[2,3]
- Novel therapies have improved survival outcomes among patients with CLL; however, evidence in older patients is limited due to low clinical trial enrollment
- This study describes treatment burden, defined as likelihood of receiving next line of therapy, among patients aged ≥75 years overall and by subgroups

METHODS

- This is a retrospective, observational study using the Flatiron Health US nationwide de-identified electronic health record (EHR)-derived database
- Patients were included if they:
  - Were aged ≥75 years at CLL/SLL diagnosis
  - Had CLL/SLL diagnosis between January 1, 2011 and October 31, 2025
  - Received ≥1 line of therapy (LOT)
  - Did not have missing treatment information
- Patients were followed from start of first-line (1L) treatment (index date) until the earliest of next treatment/second-line (2L) start, end of follow-up, death, or study end
- The primary outcome was cumulative probability of starting next treatment, including death as a competing risk
- Cumulative incidence function was used to summarize patients overall and by age group (75-79 or ≥80 years), del(17p) and/or *TP53* status (positive, negative or not tested) and immunoglobulin heavy chain variable region (IGHV) status (unmutated, mutated or not tested)
- Secondary outcomes were to descriptively summarize the most common 1L treatment by time period and age group, and the frequency of Richter transformation during follow-up
- Sensitivity analysis included patients who started 1L between 2011-2022, to allow a minimum of 3 years of potential follow-up until the data cutoff of October 31, 2025

RESULTS

- In total, 3234 patients were included; the median age was 79 years at diagnosis, 60% were male, and 73% were non-Hispanic White (**Table 1**)
- Among all patients, 1901 (59%) were aged 75-79 years at diagnosis, 1215 (38%) were 80-84 years, and 118 (4%) were ≥85 years
- Overall median follow-up was 24.7 months (interquartile range, 8.9-48.1) with decreasing follow-up observed across increasing age strata (median 35.8 months in patients aged 75-79 years, 16.2 months in 80-84 years, and 1.7 months in ≥85 years)

Table 1. Baseline Characteristics by Age at 1L Start[a]

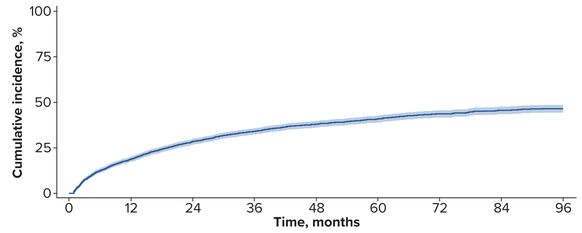
	75-79 (n=1901)	80-84 (n=1215)	≥85 (n=118)	Overall (N=3234)
Age at diagnosis, median (range), years	77 (75-79)	82 (80-84)	85 (85-85)	79 (75-85)
Time from diagnosis to index date, median (IQR), months	17.3 (2.4-39.9)	5.3 (1.3-19.3)	1.5 (1.0-2.2)	10.4 (1.7-29.5)
Sex, n (%)				
Male	1161 (61.1)	700 (57.6)	70 (59.3)	1931 (59.7)
Female	740 (38.9)	515 (42.4)	48 (40.7)	1303 (40.3)
Race and ethnicity, n (%)				
Hispanic/Latinx	80 (4.2)	44 (3.6)	10 (8.5)	134 (4.1)
Non-Latinx White	1385 (72.9)	898 (73.9)	81 (68.6)	2364 (73.1)
Non-Latinx Black	120 (6.3)	60 (4.9)	≤5	182 (5.6)
Non-Latinx Asian	13 (0.7)	8 (0.7)	≤5	23 (0.7)
Non-Latinx other	170 (8.9)	97 (8.0)	6 (5.1)	273 (8.4)
Unknown	133 (7.0)	108 (8.9)	17 (14.4)	258 (8.0)
Practice type, n (%)				
Academic	334 (17.6)	180 (14.8)	7 (5.9)	521 (16.1)
Community	1567 (82.4)	1035 (85.2)	111 (94.1)	2713 (83.9)
Disease subtype, n (%)				
CLL	1477 (77.7)	913 (75.1)	80 (67.8)	2470 (76.4)
CLL/SLL	263 (13.8)	176 (14.5)	23 (19.5)	462 (14.3)
SLL	161 (8.5)	126 (10.4)	15 (12.7)	302 (9.3)
ECOG PS at baseline, n (%)				
0	579 (30.5)	260 (21.4)	21 (17.8)	860 (26.6)
1	629 (33.1)	413 (34.0)	36 (30.5)	1078 (33.3)
2-4	198 (10.4)	216 (17.8)	28 (23.7)	442 (13.7)
Unknown	495 (26.0)	326 (26.8)	33 (28.0)	854 (26.4)
Rai stage at diagnosis, n (%)				
0	458 (24.1)	162 (13.3)	≤5	623 (19.3)
I	212 (11.2)	87 (7.2)	7 (5.9)	306 (9.5)
II	70 (3.7)	49 (4.0)	≤5	123 (3.8)
III	105 (5.5)	83 (6.8)	8 (6.8)	196 (6.1)
IV	162 (8.5)	128 (10.5)	14 (11.9)	304 (9.4)
Not documented	894 (47.0)	706 (58.1)	82 (69.5)	1682 (52.0)
del(17p) and/or *TP53* status, n (%)				
Positive	242 (12.7)	169 (13.9)	16 (13.6)	427 (13.2)
Negative	1309 (68.9)	752 (61.9)	65 (55.1)	2126 (65.7)
Not tested	350 (18.4)	294 (24.2)	37 (31.4)	681 (21.1)
IGHV status at diagnosis, n (%)				
Mutated	193 (10.2)	125 (10.3)	11 (9.3)	329 (10.2)
Unmutated	279 (14.7)	167 (13.7)	12 (10.2)	458 (14.2)
Unknown/unavailable	1429 (75.2)	923 (76.0)	95 (80.5)	2447 (75.7)
Follow-up, median (IQR), months[b]	35.8 (14.6, 61.9)	16.2 (6.5, 31.1)	1.7 (0.9, 3.7)	24.7 (8.9, 48.1)
Socioeconomic status, n (%)				
5 (highest)	428 (22.5)	277 (22.8)	28 (23.7)	733 (22.7)
4	415 (21.8)	268 (22.1)	29 (24.6)	712 (22.0)
3	352 (18.5)	200 (16.5)	22 (18.6)	574 (17.7)
2	299 (15.7)	201 (16.5)	12 (10.2)	512 (15.8)
1 (lowest)	209 (11.0)	135 (11.1)	14 (11.9)	358 (11.1)
Unknown	198 (10.4)	134 (11.0)	13 (11.0)	345 (10.7)
Insurance				
Medicare	1612 (84.8)	1013 (83.4)	90 (76.3)	2715 (84.0)
Commercial	178 (9.4)	131 (10.8)	16 (13.6)	325 (10.0)
Medicaid	27 (1.4)	10 (0.8)	7 (5.9)	44 (1.4)
Others	84 (4.4)	61 (5.0)	≤5	150 (4.6)

[a]In accordance with patient privacy requirements, values representing fewer than 6 patients are reported as ≤5. [b]Time from index date to last confirmed activities.
Abbreviations: 1L, first line; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; SLL, small lymphocytic lymphoma.

Cumulative Incidence of Next Treatment

- Using competing-risk analysis, the probability of receiving 2L increased throughout the follow-up period and did not plateau (**Figure 1**)
- Sensitivity analysis in patients who started 1L between 2011-2022 showed similar results (45.5% [95% CI, 43.3%-47.8%] at 96 months)

Figure 1. Cumulative Incidence of Next Treatment Overall

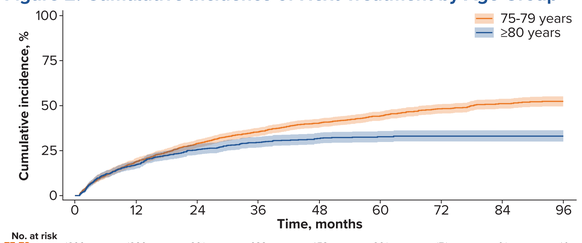


No. at risk									
Overall	3230	1917	1256	813	538	326	178	94	43

Incidence (95% CI), %	Follow-up time, months							
	12	24	36	48	60	72	84	96
Overall	18.8 (17.4-20.2)	28.5 (26.8-30.1)	34.0 (32.3-35.8)	37.9 (36.1-39.8)	40.8 (38.9-42.8)	43.7 (41.6-45.7)	45.6 (43.4-47.7)	46.5 (44.2-48.6)

- The likelihood of receiving 2L was higher in patients aged 75-79 years with 53.3% (95% CI, 50.3%-56.1%) of patients receiving 2L by the end of follow-up compared with 34.4% (95% CI, 31.4%-37.4%) of patients aged ≥80 years (**Figure 2**)

Figure 2. Cumulative Incidence of Next Treatment by Age Group

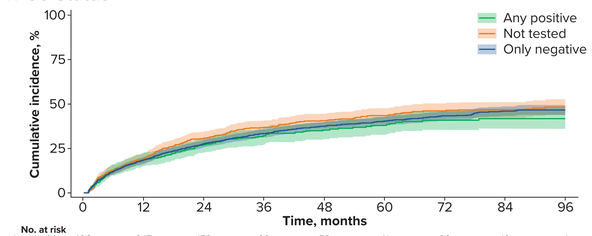


No. at risk									
75-79 years	1899	1239	891	633	453	291	171	91	40
≥80 years	1331	678	365	180	85	35	7	3	3

Incidence (95% CI), %	Follow-up time, months							
	12	24	36	48	60	72	84	96
75-79 years	19.8 (18.0-21.7)	29.9 (27.8-32.1)	36.3 (34.0-38.6)	41.1 (38.7-43.5)	45.0 (42.5-47.5)	49.1 (46.4-51.7)	52.0 (49.1-54.7)	53.3 (50.3-56.1)
≥80 years	17.2 (15.2-19.4)	26.4 (23.8-28.9)	30.7 (28.0-33.5)	33.0 (30.2-35.9)	34.1 (31.1-37.1)	34.4 (31.4-37.4)	34.4 (31.4-37.4)	34.4 (31.4-37.4)

- The likelihood of receiving 2L was also consistently higher among those not tested for del(17p) and/or *TP53* during follow-up (positive subgroup, 42.0%; negative subgroup, 46.8%; not tested at 96 months, 48.4%) (**Figure 3**)

Figure 3. Cumulative Incidence of Next Treatment by del(17p) and/or *TP53* Status

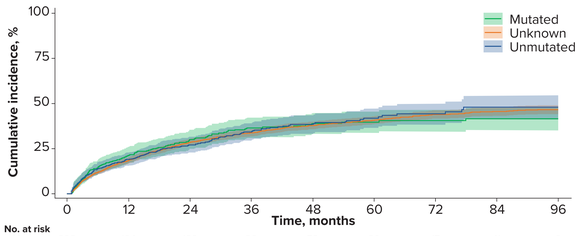


No. at risk									
Any positive	426	247	152	93	59	41	20	10	4
Not tested	681	387	252	159	106	63	40	23	11
Only negative	2123	1283	852	561	373	222	118	61	28

Incidence (95% CI), %	Follow-up time, months							
	12	24	36	48	60	72	84	96
Any positive	19.0 (15.3-23.0)	27.2 (22.7-31.7)	32.2 (27.4-37.1)	35.5 (30.4-40.6)	38.0 (32.7-43.4)	41.0 (35.3-46.7)	42.0 (36.1-47.7)	42.0 (36.1-47.7)
Not tested	19.4 (16.4-22.6)	31.0 (27.3-34.7)	37.0 (33.1-40.9)	40.7 (36.6-44.7)	43.7 (39.4-47.8)	46.2 (41.8-50.5)	46.8 (42.4-51.1)	48.4 (43.8-52.9)
Only negative	18.5 (16.9-20.3)	27.9 (25.9-29.9)	33.4 (31.3-35.6)	37.5 (35.3-39.8)	40.4 (38.0-42.8)	43.4 (40.8-45.9)	46.1 (43.4-48.8)	46.8 (44.0-49.5)

- The results were similar by IGHV mutation status until 60 months or later (**Figure 4**)

Figure 4. Cumulative Incidence of Next Treatment by IGHV Status



No. at risk									
Mutated	328	194	129	80	52	30	17	11	2
Unknown	2445	1445	946	620	416	258	142	76	38
Unmutated	457	278	181	113	70	38	19	7	3

Incidence (95% CI), %	Follow-up time, months							
	12	24	36	48	60	72	84	96
Mutated	19.0 (15.3-23.0)	27.2 (22.7-31.7)	32.2 (27.4-37.1)	35.5 (30.4-40.6)	38.0 (32.7-43.4)	41.0 (35.3-46.7)	42.0 (36.1-47.7)	42.0 (36.1-47.7)
Unknown	19.4 (16.4-22.6)	31.0 (27.3-34.7)	37.0 (33.1-40.9)	40.7 (36.6-44.7)	43.7 (39.4-47.8)	46.2 (41.8-50.5)	46.8 (42.4-51.1)	48.4 (43.8-52.9)
Unmutated	18.5 (16.9-20.3)	27.9 (25.9-29.9)	33.4 (31.3-35.6)	37.5 (35.3-39.8)	40.4 (38.0-42.8)	43.4 (40.8-45.9)	46.1 (43.4-48.8)	46.8 (44.0-49.5)

Abbreviation: IGHV, immunoglobulin heavy chain variable region.

Secondary Outcomes

- Bruton tyrosine kinase inhibitor monotherapy was the most common 1L treatment since 2014 overall and across age groups (**Table 2**)
- In addition, 55 patients (1.7%) had Richter transformation, and 52.3% of patients died during follow-up (median age at death, 85 years)

Table 2. Most Common 1L Treatment by Time Period and Age Group[a]

Index year	75-79 years, n/N (%)	80-84 years, n/N (%)	≥85 years, n/N (%)	Overall, n/N (%)
2011-2013	Rituximab mono, 40/98 (40.8)	Other, 33/74 (44.6)	Other, ≤5	Rituximab mono, 67/180 (37.2)
2014-2019	BTKi mono, 310/857 (36.2)	BTKi mono, 191/506 (37.7)	BTKi mono, 16/50 (32.0)	BTKi mono, 517/1413 (36.6)
2020-2022	BTKi mono, 303/555 (54.6)	BTKi mono, 180/338 (53.3)	BTKi mono, 15/29 (51.7)	BTKi mono, 498/922 (54.0)
2023-2025	BTKi mono, 197/391 (50.4)	BTKi mono, 170/297 (57.2)	Rituximab mono, 13/31 (41.9)	BTKi mono, 379/719 (52.7)

[a]In accordance with patient privacy requirements, values representing fewer than 6 patients are reported as ≤5.
Abbreviations: 1L, first line; BTKi, Bruton tyrosine kinase inhibitor; mono, monotherapy.

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DISCLOSURES

DAE: Honoraria: BeOne Medicines, Ltd; Consulting or advisory role: BeOne Medicines, Ltd, ADC Therapeutics; Speakers bureau: Incyte, AstraZeneca. **AA:** No disclosures. **XW:** Employment: BeOne Medicines, Ltd (current), Flatiron Health (former); Stock or other ownership: BeOne Medicines, Ltd, Roche. **EKS:** Employment: BeOne Medicines, Ltd; Stock or other ownership: BeOne Medicines, Ltd, Roche. **DvB:** Employment: BeOne Medicines, Ltd; Stock or other ownership: BeOne Medicines, Ltd, Pfizer, GSK, Nurix. **JMR:** Honoraria: Aptitude, Curio Science, Dava Oncology, MJH Life Sciences, Ideology Health; Consulting or advisory role: AbbVie, AstraZeneca, ADC Therapeutics, BeOne Medicines, Ltd, BMS, Epizyme, Genentech, GenMab, Loxo Oncology, Janssen, Johnson and Johnson, Morphosys, Pharmacyclics, Pfizer, TG Therapeutics, SeaGen, Verastem; Research funding: Acerta, AbbVie, BeOne Medicines, Ltd, Epizyme, Janssen, Johnson and Johnson, Loxo Oncology, Oncternal Therapeutics, Pharmacyclics, VelosBio, Merck; Travel, accommodations, expenses: Curio Science, DAVA Pharmaceuticals, Loxo, Merck. **DY, RW:** Employment and may own stock: BeOne Medicines, Ltd.

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