Real-world treatment and outcomes among older adults with chronic lymphocytic leukemia before the novel agents era

Chronic lymphocytic leukemia (CLL) is the most common leukemia among adults in Western countries, with a median age at diagnosis of 70 years.[1] Until 2014, chemoimmunotherapy combinations were the mainstay treatment, particularly for physically fit patients.[2,3] However, older individuals or those with comorbid conditions may be less likely to tolerate standard CLL chemoimmunotherapy combinations. It is important to establish a baseline understanding of real-world CLL treatments and outcomes prior to the introduction of novel agents, as this would allow for a better understanding of unmet needs, particularly among older patients in the pre-novel therapy era, and also inform future comparative effectiveness studies.[4] Current literature provides limited data about real-world treatment patterns and survival among older CLL patients. To address these gaps in the literature, we utilized comprehensive prescription and medical insurance claims linked with cancer registry data to analyze both first-line and second-line treatment patterns as well as survival outcomes in older adults newly diagnosed with CLL, in the time period (2007-2013) that immediately predated FDA approval of novel agents. We also stratified outcomes by age (66-74 "younger seniors" *vs.* ≥75 years "older seniors").

Our retrospective cohort study used 2007-2013 Surveillance, Epidemiology, and End Results (SEER) data linked with Medicare files to compare treatment patterns, time-to-treatment initiation, and overall and CLL-specific survival from first-line and second-line treatments among Medicare beneficiaries aged >65 years who were newly diagnosed with CLL between 2007 and 2011. The SEER registries capture newly diagnosed cancer patients, covering about 28% of the U.S. population.[5] The SEER-Medicare files utilized in our study included all SEER patients from 2007 through 2011 who had fee-for-service Medicare claims (inpatient, outpatient, physician, skilled nursing facility care, home health, hospice, pharmacy [Part D] claims) linked from 2007 through 2013.

Details of the sample selection process may be found in *Online Supplementary Figure S1*. Our final study sample consisted of 3214 newly diagnosed CLL patients. Initial treatment pattern outcomes consisted of the percentage of patients receiving a CLL treatment, mean time to first-line treatment initiation, and the type of treatment regimen initiated. A full list of CLL treatments may be found in *Online Supplementary Table S1*. Time to first-line treatment initiation was defined as the time elapsed between the index (diagnosis) date and the date of the first claim for a CLL treatment. Type of treatment regimen was categorized as chlorambucil monotherapy, rituximab monotherapy, rituximab-containing chemoimmunotherapy combination, or other chemotherapy. A therapy was considered part of the first-line treatment regimen if it was received within 60 days of the initial drug claim.[6,7]

We also examined second-line treatments, defined as re-initiation of at least one or all of the agents in the first-line treatment regimen following a treatment-free interval of >180 days, or the addition of a new treatment that was not part of the first-line treatment regimen. The second-line treatment start date was defined as the date on which the re-initiated therapy was administered or filled or the date on which the new treatment was added. Time to second-line treatment initiation was defined as the time elapsed between the index (diagnosis) date and the start of the second-line treatment date.

Survival outcomes included overall survival (OS) and CLL-specific survival from first-line and second-line CLL

Table 1. Treatment patterns of elderly Medicare patients newly diagnosed with chronic lymphocytic leukemia, by age group.

	Overall		Age <75		Age ≥75		P*
	n	%	n	%	n	%	
All CLL patients	3214	100	1243	39	1971	61	
Received first-line treatment	1047	32.6	476	38.3	571	29.0	<0.001*
Received second-line treatment	387	12.0	176	14.2	211	10.7	0.004*
Patients receiving first-line treatment	1047	100	476	100	571	100	
Type of first treatment among those treated							<0.001†
Chlorambucil only	163	15.6	43	9.0	120	21.0	
Rituximab only	268	25.6	95	20.0	173	30.3	
Rituximab-containing chemoimmunotherapy combination	510	48.7	296	62.2	214	37.5	
Other chemotherapy	106	10.1	42	8.8	64	11.2	
Patients receiving second-line treatment	387	100	176	100	211	100	
Type of second treatment among those treated							0.014†
Chlorambucil only	35	9.0	#	#	27	12.8	
Rituximab only	118	30.5	55	31.3	63	29.9	
Rituximab-containing chemoimmunotherapy combination	158	40.8	82	46.6	76	36.0	
Other chemotherapy	76	19.6	31	17.6	45	21.3	

*P-values reflect the results of t-tests. †P-values reflect the results of chi-square tests. #Cells with counts of less than 11 are not reported in compliance with the National Cancer Institute data use agreement. CLL: chronic lymphocytic leukemia.

treatment. We also examined 1-year and 2-year OS rates. CLL-specific survival was defined as the net survival measure representing cancer survival in the absence of other causes of death. Kaplan-Meier estimates were used to examine OS from first-line and second-line treatment dates among patients receiving these treatments.[8] Cox regression models examined factors associated with OS and CLL-specific survival from the first treatment date and second-line treatment date among treated patients.[9]

Online Supplementary Tables S2 and *S3* provide sociodemographic and clinical characteristics, by age group and treatment status, respectively, for our final sample. Median follow up was 36.1 months from CLL diagnosis. As shown in Table 1, 1047 (32.6%) of the overall patient sample received first-line treatment, with lower rates of treatment in the older seniors group (29.0% *vs.* 38.3%; $P<0.001$). However, the older seniors group had a shorter median time to first treatment (4.4 *vs.* 6.8 months; $P<0.001$), (*data not shown)*. Rituximab-containing chemoimmunotherapy combinations were the most common treatment approaches overall (utilized in nearly half of patients receiving first-line treatment), yet significant differences were observed in the distribution of treatment approaches between the two age groups ($P<0.001$). For example, a higher proportion of the older seniors group (*vs.* younger group) received monotherapy with either chlorambucil (21.0% *vs.* 9.0%) or rituximab (30.3% *vs.* 20.0%).

Twelve percent of patients received second-line treatment; again, rates were lower in the older seniors group (10.7% *vs.* 14.2%; $P=0.004$). Among patients receiving second-line treatment, the median time from CLL diagnosis to initiation of the second-line treatment was 21.8 months (*data not shown)*. Similar to the findings for first-line treatment, rituximab-containing chemoimmunotherapy combinations were the most common second-line treatments (40.8%).

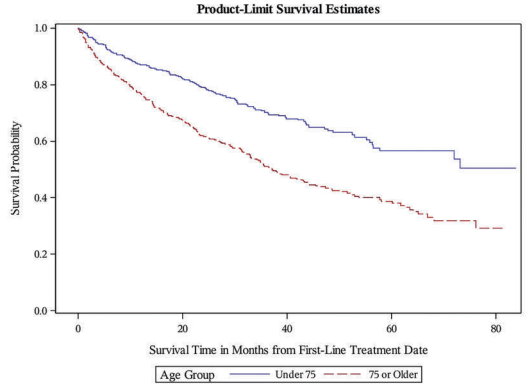
Table 2. Survival rates among elderly Medicare patients newly diagnosed with chronic lymphocytic leukemia, by age group.*

	Overall	Age <75	Age ≥75
From first-line treatment of CLL			
N	1047	476	571
Overall survival			
1-year	81.4%	87.0%	76.9%
2-year	69.3%	79.0%	61.7%
CLL-specific survival			
1-year	88.0%	91.3%	85.3%
2-year	81.4%	87.3%	76.6%
From second-line treatment of CLL			
N	387	176	211
Overall survival			
1-year	71.8%	79.6%	65.6%
2-year	57.5%	65.4%	51.3%
CLL-specific survival			
1-year	82.8%	89.2%	77.5%
2-year	74.1%	80.5%	68.9%

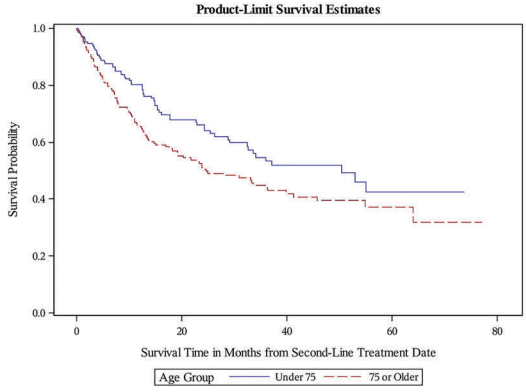
*Log-rank tests comparing Kaplan-Meier curves for age strata equivalence in survival over time were significant for all comparisons except CLL-specific survival after second-line treatment ($P=0.056$). CLL: chronic lymphocytic leukemia.

The median OS from first-line treatment initiation and second-line treatment initiation was 52.4 months and 33.7 months, respectively (*data not shown)*. Estimated 1-year and 2-year OS rates after first-line treatment initiation were 81.4% and 69.3%, respectively (Table 2). OS rates after second-line treatment initiation were 71.8% at 1 year and 57.5% at 2 years. Patients in the older seniors group had a 1-year OS rate of 66.7% and 2-year OS rate of 61.7%, whereas those in the younger seniors group had a 1-year OS rate of 87.0% and 2-year OS rate of 79.0%. Similar patterns were observed for OS rates from the time of second-line treatment. Unadjusted Kaplan-Meier curves for OS from first- and second-line treatments are shown in Figure 1.

Regression results are displayed in *Online Supplementary Table S4*. Among patients receiving first-line treatment, older age was associated with worse OS (hazard ratio [HR],1.81; 95% confidence interval [CI],1.46 to 2.24). Additionally, male sex, a Northeast location relative to the West, receiving Medicare Part D low-income subsidies, higher National Cancer Institute (NCI) comorbidity index score,[10] and presence of disability were associated with worse OS. Receipt of rituximab monotherapy (HR, 0.69; 95% CI, 0.51 to 0.91) or rituximab-containing chemoimmunotherapy combinations (HR, 0.64; 95% CI, 0.49 to 0.84), compared to chlorambucil monotherapy, were associated with better OS after first-line treatment. As with first-line treatment, older age was associated with worse OS among patients receiving second-line treatment.



Note: Log-rank $P<0.001$



Note: Log-rank $P<0.019$

Figure 1. Overall survival from first-line treatment date and second-line treatment date, by age group.

Among patients receiving first-line treatment, older age (HR,1.81; 95% CI,1.34 to 2.44), male sex, receiving Medicare Part D low-income subsidies, and higher NCI comorbidity index score were associated with worse CLL-specific survival outcomes. Receipt of rituximab or rituximab-containing chemoimmunotherapy combinations compared to chlorambucil monotherapy was associated with better CLL-specific survival outcomes. Similarly, older age was associated with worse CLL-specific survival among patients receiving second-line treatment (HR, 1.86; 95% CI, 1.15 to 2.99).

The study herein provides detailed observational data regarding treatment patterns and outcomes of CLL patients treated in the pre-novel therapy era with both first-line and second-line treatments. Such data will be an important baseline for future evaluations of novel therapies. We found that approximately one-third of newly diagnosed elderly CLL patients received first-line treatment, over a median follow-up of 3 years. Among those who received CLL treatment, approximately 37% progressed to a relapse/refractory phase, with a median time to second-line treatment of 22 months. Rituximab combination therapies were common for both first-line and second-line treatment. In our study 21% of older seniors received chlorambucil as a first-line treatment.

Of note, patients aged ≥75 years were less likely to initiate treatment compared to younger seniors. When they did initiate treatment, they were more likely to receive monotherapy with chlorambucil or rituximab. These findings may be related to data from clinical trials suggesting a minimal benefit of adding rituximab to chlorambucil monotherapy or to fludarabine and cyclophosphamide in patients older than 65 years.[11,12] Given that novel therapies, including ibrutinib[13] and the combination of the glycoengineered anti-CD20 antibody obinutuzumab and chlorambucil[14] have shown superior outcomes as compared to chlorambucil monotherapy in clinical trials,[13,14] these agents may represent promising new therapies for current and future patients similar to those included in our study.

In addition to having lower rates of treatment, treated patients aged ≥75 years had significantly lower OS as compared to younger seniors, and this discrepancy persisted even after controlling for socioeconomic, clinical, and treatment characteristics. This older population is prone to a greater incidence and severity of comorbidities, as well as disease- and infection-related death, all of which may lead to delays in therapy initiation and poorer outcomes.[15-18] OS rates among all treated patients were modest (median 52.4 months for first-line therapy and 33.7 months for second-line therapy). Although our study does not permit causal inferences, we observed that rituximab monotherapy and rituximab-containing chemoimmunotherapy combinations were associated with favorable survival outcomes when compared to chlorambucil monotherapy in the front-line setting.

Our study has some limitations. First, we utilized registry and claims data and did not have access to all relevant prognostic factors, such as β2-microglobulin, lactate dehydrogenase, white cell count, or molecular and genetic abnormalities (e.g., presence of Del(17p)/TP53 mutation), which could have influenced treatment choice or survival outcomes. Additionally, the SEER-Medicare registry does not contain staging information for leukemia patients and our markers for disease severity (e.g., patients with claims-based diagnoses of anemia and thrombocytopenia) may not have been an adequate proxy of severity for all the patients in our study. If these unmeasured confounders correlated with the variables (e.g., age group, treatment group) included in our multivariable survival model, our estimates would be biased.

In this population-based study of Medicare beneficiaries diagnosed with CLL in the years prior to the novel therapy era, we observed modest overall and CLL-specific survival among patients treated in both first-line and relapse-refractory contexts. Older seniors had lower rates of treatment, were more commonly treated with monotherapies, and had poorer disease-specific and OS outcomes compared to younger patients. As longitudinal data on novel therapies continue to accumulate, future studies should examine CLL outcomes to investigate how results obtained in recent landmark clinical trials translate into clinical practice.

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