Time to Next Treatment, Health Care Resource Utilization, and Costs Associated with Ibrutinib Use Among U.S. Veterans with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: A Real-World Retrospective Analysis

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ABSTRACT

BACKGROUND: Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is the most common adult leukemia, accounting for $\approx 37\%$ of all leukemias in the United States. Limited real-world evidence is available on the outcomes of ibrutinib use among previously untreated patients in the U.S. Veterans Health Administration (VHA) population diagnosed with CLL/SLL.

OBJECTIVES: To (a) evaluate time to next treatment (TTNT) among U.S. veterans with CLL/SLL who initiated ibrutinib versus chemoimmunotherapy (CIT) in first line (1L) and 1L ibrutinib versus ibrutinib in later lines (2L+) and (b) compare health care resource utilization (HRU) and costs between the 1L ibrutinib and CIT cohorts.

METHODS: Adults with CLL/SLL and claims for 1L single-agent ibrutinib or CIT (index date = first prescription claim date) were included from Veterans Health Administration Data (April 1, 2013–March 31, 2018). A subset of the CIT 1L cohort with evidence of ibrutinib in 2L/3L was defined as the ibrutinib 2L+ cohort. Kaplan-Meier curves and Cox proportional hazard models were used to evaluate TTNT, and generalized linear models were used to determine all-cause per patient per month (PPPM) HRU and costs during 1L among propensity score-matched (PSM) cohorts.

RESULTS: After PSM, 614 patients were included in each of the 1L ibrutinib and 1L CIT cohorts, and 149 were included in each of the 1L ibrutinib and 2L+ ibrutinib cohorts. The 1L ibrutinib cohort had significantly longer TTNT compared with each of the 1L CIT and 2L+ ibrutinib cohorts ($P < 0.0001$ and $P = 0.0001$, respectively) and was less likely to have a next line of treatment than the CIT 1L cohort (HR = 0.52; 95% CI = 0.42–0.65; $P < 0.0001$) and the 2L+ ibrutinib cohort (HR = 0.39; 95% CI = 0.22–0.69; $P = 0.0012$). The 1L ibrutinib cohort had significantly fewer inpatient visits (rate ratio [RR] = 0.38; 95% CI = 0.28–0.52; $P \leq 0.05$) and outpatient visits PPPM (RR = 0.72; 95% CI = 0.68–0.77; $P \leq 0.5$) compared with the CIT 1L cohort. Additionally, the 1L ibrutinib cohort had \$7,308 significantly lower monthly medical costs (95% CI = –\$9,892 to –\$4,895; $P \leq 0.05$) versus the 1L CIT cohort, resulting in comparable monthly total health care cost (medical and pharmacy) between real-world 1L patients treated by ibrutinib and CIT (–\$2,160; 95% CI = –\$4,840–\$347; $P > 0.05$).

CONCLUSIONS: These findings demonstrate that among U.S. veterans with CLL/SLL, 1L ibrutinib use was associated with significantly longer TTNT versus that of 1L CIT. Similarly, early treatment with ibrutinib was associated with longer TTNT as compared to ibrutinib use in later lines of therapy. Moreover, 1L ibrutinib was associated with lower HRU and medical costs compared with 1L CIT, completely offsetting the higher pharmacy costs related to 1L ibrutinib treatment.

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What is already known about this subject

- Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is the most common adult leukemia, accounting for $\approx 37\%$ of all leukemias in the United States.
- Targeted therapies, like ibrutinib, have changed the therapeutic paradigm for CLL achieving improved outcomes with acceptable toxicity.

What this study adds

- 1L ibrutinib treatment, compared with chemoimmunotherapy or later administration of ibrutinib, is associated with significantly longer time to new treatment among U.S. veterans.
- Lower health care resource utilization and medical costs with 1L ibrutinib offset higher pharmacy costs incurred by U.S. veterans.

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) account for $\approx 7\%$ of newly diagnosed non-Hodgkin lymphoma (NHL) cases.¹ In 2019, the number of cases of newly diagnosed CLL in the United States was estimated to be 20,720, accounting for 1.2% of all new cancer cases.² Although some patients have a highly aggressive course, others have indolent disease that progresses slowly over a period of years and does not require immediate treatment.^{3,4} The most unfavorable prognosis is associated with the patients carrying deletion 17p, deletion 11q, unmutated immunoglobulin heavy chain variable gene (*IGHV*), or mutation of the *TP53* gene (*mTP53*).^{5,6}

The etiology of CLL/SLL is unknown. However, CLL incidence is 2 times higher in men, and nearly 70% of patients are aged ≥ 65 years at diagnosis.⁷ Additionally, positive family history of CLL, European ancestry, and exposure to chemicals such as Agent Orange and pesticides are considered risk factors of CLL.⁸ Considering these risk factors, veterans have a higher risk for CLL as they are predominantly male, aged ≥ 65 years, and have higher incidence of exposure to Agent Orange or other herbicides during military service.⁹

Chemoimmunotherapy (CIT) regimens—such as fludarabine, cyclophosphamide, and rituximab (FCR); bendamustine and rituximab (BR); and the combination of chlorambucil and cluster of differentiation (CD)20 antibodies—represented progress in the treatment of CLL with improved response and prolonged survival rates.^{10,11} Although CIT still plays a role in the treatment of previously untreated CLL patients, without *TP53* mutations, del17p and unmutated (U-)CLL cytogenetics, the treatment landscape has changed considerably with the introduction of oral targeted therapies.^{10,12-14}

In 2014, the U.S. Food and Drug Administration (FDA) approved ibrutinib, a once-a-day oral inhibitor of Bruton's tyrosine kinase, initially for the treatment of CLL after receiving ≥ 1 previous therapies and subsequently as a first-line (1L) treatment for patients with del(17p). In 2016, the FDA expanded approval for ibrutinib as a 1L treatment for all patients, based on the RESONATE-2 study.^{15,16} The results of additional clinical trials demonstrate that ibrutinib improves overall response, progression-free survival, and overall survival among treatment-naïve CLL patients when compared with other commonly used chemoimmunotherapy regimens including FCR, BR, or the combination of chlorambucil and obinutuzumab.^{11,15,17-20} Until recently, ibrutinib was the only preferred regimen listed in National Comprehensive Cancer Network guidelines for 1L CLL treatment regardless of age, fitness, or comorbidities.¹⁶

Just as therapeutic approaches for CLL have evolved from CIT to targeted therapies, health care resource utilization and economic burden associated with CLL therapy will also evolve. The resource utilization and economic burden of CLL are significant, with monthly per-patient costs varying greatly by care setting, treatment regimen, and rate of adverse events (AEs).²¹⁻²⁴ Compared with 2011, the number of people living with CLL in the United States is expected to increase by more than 50% by 2025 due to improved treatment options and higher survival rates.^{2,25}

Given the limited real-world evidence of ibrutinib treatment among patients with CLL/SLL in the Veterans Administration (VA) population, the present study aimed to determine if treatment with ibrutinib single-agent in 1L was beneficial in extending time to next treatment (TTNT) when compared with 1L CIT and ibrutinib in the second and third line (2L+) among veterans with CLL/SLL. Additionally, our study compared health care resource utilization (HRU) and costs between 1L ibrutinib and 1L CIT cohorts.

Methods

Study Design and Data Source

This was a retrospective cohort study ([Supplementary Figure 1](#), available in online article) utilizing pharmacy and medical claims from the VHA database during the period of April 1, 2013, through March 31, 2018. The VHA is the largest

integrated health care system in United States, providing care at 1,250 health care facilities, including 172 VA medical centers and 1,069 outpatient sites of care of varying complexity to more than ≈ 9 million veterans across the country.²⁶

Study Population

Patients were required to have ≥ 2 claims with a diagnosis code for CLL (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM]: 204.1; *International Classification of Diseases, 10th Revision, Clinical Modification* [ICD]-10-CM: C91.1) or SLL (ICD-9-CM: 200.8; ICD-10-CM: C83.0) at any time during the study period (April 1, 2013–March 31, 2018). The first CLL/SLL diagnosis date was designated as the first observed CLL/SLL diagnosis date. Also, patients were required to have ≥ 1 prescription claim for ibrutinib single-agent or any combination of National Comprehensive Cancer Network–recommended chemotherapy agents (bendamustine, chlorambucil, cyclophosphamide, cytarabine, doxorubicin, fludarabine, lenalidomide, oxaliplatin, pentostatin, vincristine, and cladribine) with an immunotherapy agent (alemtuzumab, obinutuzumab, ofatumumab, and rituximab) for CLL/SLL during the identification period (April 1, 2014–December 31, 2017) following the first observed CLL/SLL diagnosis date.

The identification period was chosen to capture the use of ibrutinib following U.S. approval. Ending the identification period 3 months before the end of data availability was intentional, to allow for ≥ 3 months of follow-up data accumulation by the end-of-study period. The first prescription claim for ibrutinib single-agent or CIT at any time in the identification period following the first CLL/SLL diagnosis (initial diagnosis date) was designated as the index date. For combination regimens, agents prescribed within 30 days of the index date constituted 1L. Only the patients who were prescribed ibrutinib single-agent were considered, and those who received CD20 agents together with ibrutinib were excluded. Patients were also required to be aged ≥ 18 years on the index date and have continuous health plan enrollment with medical and pharmacy benefits for ≥ 12 months before and ≥ 30 days after the index date. Patients were followed until death, end of continuous enrollment, or the end-of-study period, whichever occurred the earliest.

Patients were excluded from the study if they had evidence of ibrutinib or other CIT at any time before the index date and after the first diagnosis date or had evidence of pregnancy (ICD-9-CM: 630.xx-679.xx, v22.x-v24.x) or end-stage renal disease (ICD-9-CM: 585.6) at any time during the study period. Based on the 1L treatment received patients were classified into the 1L ibrutinib cohort or 1L CIT cohort. In the 1L CIT cohort, the subgroup of patients treated with a single-agent ibrutinib in the 2L/3L and with continuous enrollment of ≥ 12 months before and ≥ 30 days after the index date was included in the 2L+ ibrutinib cohort (index date was defined as the date

of initiating ibrutinib treatment, as presumed from the first claim for the drug).

Demographic and Clinical Characteristics

Demographic characteristics including age, sex, and race were measured on the index date and the year of the index treatment was reported. Quan-Charlson Comorbidity Index (Quan-CCI) score ([Supplementary Table 1](#), available in online article), clinical conditions of interest (abdominal pain, anemia, autoimmune hemolytic anemia, enlarged lymph nodes, fatigue/weakness, fever, lymphocytosis, thrombocytopenia, weight loss, atrial fibrillation, and major bleeding; diagnosis codes can be found in [Supplementary Table 2](#), available in online article), and baseline medications related to common morbidities in the VHA population (antiplatelet drugs, anticoagulant agents, dexamethasone, prednisone, methylprednisolone, proton pump inhibitors, and antidepressants) were examined and reported in the 12-month pre-index period. Major bleeding was defined by the consensus report from the Bleeding Academic Research Consortium.²⁷

Outcome Measures

TTNT was defined as the time from the index date to the initiation of next-line treatment. Patients lost to follow-up or without evidence of next-line treatment were censored. The 1L therapy period spanned the index date through the earliest of addition or subtraction of any agent to the index regimen or initiation of a non-index regimen or resumption of the index regimen after a >90-day gap or death/end of continuous enrollment/study end.²⁴ TTNT was compared between the 1L ibrutinib and 1L CIT cohorts as well as between 1L ibrutinib and 2L+ ibrutinib cohorts.

All-cause HRU and health care costs per patient per month (PPPM) were measured during the 1L therapy period for outpatient (including ER visits), inpatient, pharmacy services, and avoidable hospitalizations, as defined by the Agency for Healthcare Research and Quality (AHRQ) Prevention Quality Indicators (PQI; list of avoidable hospitalizations along with the diagnosis codes can be found in [Supplementary Table 3](#), available in online article).²⁸ Among the causes for avoidable hospitalizations, defined by AHRQ PQI, are asthma, bacterial pneumonia, chronic obstructive pulmonary disease, dehydration, diabetes, heart failure, hypertension, perforated appendix, or urinary tract infection, outpatient visits resulting in hospitalization (outpatient visits followed by inpatient visits on the same day), and outpatient visits related to administration of antineoplastic agents. All-cause HRU and costs were compared between the 1L ibrutinib and 1L CIT cohorts only. As this study is a total cost of care analysis, all medical and pharmacy costs related to the disease and its treatment encountered by patients in each cohort were analyzed.

Statistical Analysis

Descriptive statistics were provided for all study variables (means and standard deviations [SDs] for continuous variables, numbers and percentages for categorical variables), among all study cohorts. Chi-square and Student t-tests were conducted to evaluate the statistical significance for categorical and continuous variables, respectively.

To reduce potential selection bias, 1-to-1 propensity score matching (PSM) was performed between the 1L ibrutinib and 1L CIT cohorts and between the 1L ibrutinib and 2L+ ibrutinib cohorts, using nearest neighbor matching with a caliper width of 0.2 of the SD of the logit of the propensity score. Covariates used in propensity score calculation included demographics, index year, clinical conditions of interest (including those related to potential ibrutinib toxicity), and baseline medications. After PSM, the adequacy of the matching procedure was assessed by standardized difference (STD) of the baseline characteristics between the 2 groups. Characteristics with STD <10% were considered well balanced.²⁹

Kaplan-Meier (KM) curves and Cox proportional hazards models were used to evaluate the TTNT in the matched cohorts. Covariates were further adjusted in the models based on potential confounders in the literature along with covariates that were not balanced after PSM. Covariates adjusted in the Cox model for 1L ibrutinib versus 1L CIT included baseline inpatient length of stay (LOS) and all-cause total costs. Covariates adjusted in the Cox model for 1L ibrutinib versus 2L+ ibrutinib included baseline demographic and clinical characteristics (age, race, index year, anemia, autoimmune hemolytic anemia, atrial fibrillation, dexamethasone), number of inpatient visits PPPM, number of outpatient visits PPPM, inpatient LOS, baseline all-cause inpatient, outpatient and total costs.

Generalized linear models (GLM) were used to estimate the rate ratios (RR) and mean differences for HRU and costs PPPM, respectively, among the matched 1L ibrutinib and 1L CIT cohorts. Additionally, 95% confidence intervals (CIs) were presented using the nonparametric bootstrap procedure with the percentile CI method. Similar to the Cox model for 1L ibrutinib versus 1L CIT cohorts, baseline LOS and all-cause total costs were adjusted in the GLM.

Sensitivity Analysis

To ensure the robustness of the results in the main analysis, 3 sensitivity analyses were conducted. First, the PSM was repeated in all the study cohorts, adjusting for the index quarter of treatment (instead of index year), along with the demographics and clinical characteristics adjusted in the main analysis. Additionally, KM analysis, Cox modeling, and GLMs were repeated in these matched cohorts. Second, study cohort matching was performed using the inverse probability of treatment weighting (IPTW) approach, adjusting for the demographics, clinical characteristics, and index quarter. KM

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TABLE 1 Comparison of Baseline Demographic, Clinical Characteristics, and Medications After PSM for the 1L Ibrutinib Versus 1L CIT and 1L Ibrutinib Versus 2L+ Ibrutinib Cohorts

Baseline Characteristics	Ibrutinib 1L (n = 614)		CIT 1L (n = 614)		P Value	STD, %	Ibrutinib 1L (n = 149)		Ibrutinib 2L+ (n = 149)		P Value	STD, %
	Mean/n	SD/%	Mean/n	SD/%			Mean/n	SD/%	Mean/n	SD/%		
Age (in years)	71.84	10.42	71.30	10.58	0.3684	5.14	73.89	12.18	70.50	9.94	0.0091	30.42
< 60	38	6.19	45	7.33	0.4262	4.54	NA	NA	13	0.087248	0.2578	13.10
60-64	50	8.14	52	8.47	0.8362	1.18	NA	NA	14	0.09396	0.2778	12.56
65-69	197	32.08	201	32.74	0.8073	1.39	44	29.53	46	30.87	0.8008	2.91
70-74	159	25.90	151	24.59	0.5992	3.00	32	21.48	42	28.19	0.1800	15.53
75-79	82	13.36	79	12.87	0.7998	1.45	17	11.41	13	8.72	0.4412	8.90
≥80	88	14.33	86	14.01	0.8700	0.93	39	26.17	21	14.09	0.0093	30.37
Gender												
Male	610	99.35	607	98.86	0.3636	5.18	148	99.33	147	98.66	0.5617	6.70
Race												
Caucasian	488	79.48	482	78.50	0.6743	2.40	120	80.54	113	75.84	0.3261	11.36
African American	82	13.36	90	14.66	0.5107	3.75	19	12.75	26	17.45	0.2574	13.10
Other or Unknown	44	7.17	42	6.84	0.8230	1.28	NA					
Index year												
2014	86	14.01	97	15.80	0.3781	5.03	17	0.114094	NA	NA	0.1578	16.37
2015	130	21.17	131	21.34	0.9444	0.40	24	16.11	29	19.46	0.4488	8.75
2016	194	31.60	195	31.76	0.9511	0.35	51	34.23	54	36.24	0.7160	4.20
2017	204	33.22	191	31.11	0.4271	4.53	57	38.26	56	37.58	0.9050	1.38
Quan Charlson Comorbidity Index Score	3.54	2.01	3.71	2.07	0.1466	8.29	3.80	2.24	3.80	2.19	0.9958	0.06
Clinical conditions of interest												
Abdominal pain	45	7.33	42	6.84	0.7386	1.90	13	8.72%	NA	NA	0.6703	4.92
Anemia	158	25.73	165	26.87	0.6500	2.59	40	26.85	56	37.58	0.0473	23.05
Autoimmune hemolytic anemia	12	1.95	14	2.28	0.6918	2.26	NA	NA	NA	NA	0.3099	11.75
Enlarged lymph nodes	112	18.24	105	17.10	0.6005	2.99	32	21.48	28	18.79	0.5634	6.68
Fatigue/weakness	49	7.98	45	7.33	0.6677	2.45	22	14.77	20	13.42	0.7392	3.85
Fever	12	1.95	16	2.61	0.4445	4.36	NA	NA	NA	NA	0.4537	8.66
Lymphocytosis	19	3.09	19	3.09	1.0000	0.00	NA	NA	NA	NA	1.0000	0.00
Thrombocytopenia	82	13.36	89	14.50	0.5640	3.29	25	16.78	26	17.45	0.8778	1.78
Weight loss	40	6.51	43	7.00	0.7331	1.94	16	10.74	14	9.40	0.7002	4.45
Atrial fibrillation	49	7.98	52	8.47	0.7553	1.78	17	11.41	NA	NA	0.1578	16.37
Major bleeding	26	4.23	24	3.91	0.7727	1.65	NA					
Baseline medications												
Antiplatelet drugs	141	22.96	140	22.80	0.9458	0.39	27	18.12	29	19.46	0.7668	3.42
Anticoagulant agents	52	8.47	60	9.77	0.4278	4.52	18	12.08	19	12.75	0.8606	2.03
Dexamethasone	20	3.26	26	4.23	0.3672	5.14	18	12.08	30	20.13	0.0586	21.97
Prednisone	83	13.52	87	14.17	0.7410	1.88	34	22.82	36	24.16	0.7846	3.16
Methylprednisolone	19	3.09	16	2.61	0.6069	2.93	NA	NA	12	8.05	0.6577	5.12
Proton pump inhibitors	217	35.34	208	33.88	0.5893	3.08	61	40.94	59	39.60	0.8133	2.73
Antidepressants	30	4.89	29	4.72	0.8939	0.76	NA					

1L = first line; 2L+ = second line or later; CIT = chemoimmunotherapy; NA = not available; PSM = propensity score-matched; SD = standard deviation; STD = standardized difference.

analysis, Cox modeling, and GLMs were repeated in these matched cohorts.

Results

After applying the sample selection criteria, there were 787 patients in the 1L ibrutinib cohort and 1,039 patients in the 1L

CIT cohort ([Supplementary Table 4](#), available in online article). Of these 1L CIT patients, 597 patients initiated BR (57.5%), 150 initiated FCR (14.4%), and 94 initiated chlorambucil-obinutuzumab (9.0%). Additionally, among the 1L ibrutinib patients, 146 (18.6%) received 2L therapy, of which 92 (63.0%) restarted ibrutinib as a 2L regimen (after a >90-day gap). In

FIGURE 1 Comparison of TTNT Between 1L Ibrutinib and 1L CIT

Patient at risk	6 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months
Ibrutinib 1L, n (%)	510 (83.1)	361 (58.8)	247 (40.2)	156 (25.4)	99 (16.1)	63 (10.3)	24 (3.9)	1 (0.2)
CIT 1L, n (%)	453 (73.8)	322 (52.4)	237 (38.6)	161 (26.2)	82 (13.4)	51 (8.3)	23 (3.7)	2 (0.3)

^aHazard ratios were calculated using Cox proportional hazards regression models in the propensity score-matched cohorts.

1L=first line; 2L=second line; CI=confidence interval; HR=hazard ratio; CIT=chemoimmunotherapy; TTNT=time to next treatment.

contrast, among the 1L CIT patients, 409 (39.4%) received a subsequent line of therapy, of which 185 (45.2%) had ibrutinib as the 2L/3L regimen.

Baseline Characteristics Before PSM

Compared with the CIT 1L cohort, patients in the 1L ibrutinib cohort were significantly older, and the majority were male and Caucasian. Additionally, the 1L ibrutinib cohort had significantly lower mean Quan-CCI scores and a lower proportion of patients with anemia, enlarged lymph nodes, fatigue/weakness, fever, and lymphocytosis, as well as a significantly lower proportion of patients with baseline medications including anticoagulant agents, dexamethasone, prednisone, and methylprednisolone versus the CIT 1L cohort ([Supplementary Table 1](#), available in online article).

A similar trend was observed when demographic and clinical characteristics between the 1L ibrutinib versus 2L+ ibrutinib cohorts were compared ([Supplementary Table 1](#)).

Baseline Characteristics After PSM

After PSM, a total of 614 patients each were included in the 1L ibrutinib and 1L CIT cohorts and were well balanced with respect to all demographic and clinical characteristics examined (Table 1). Additionally, 149 patients were included in each of the 1L ibrutinib versus 2L+ ibrutinib cohorts, the cohorts were well balanced for most baseline characteristics. The remaining differences, due to limited sample size, were adjusted during multivariate analysis of outcomes.

The mean length of follow-up period was 19.8 months (SD 12.0 months; median 17.6 months) in 1L ibrutinib and 21.5 months (SD 12.8 months; median 20.2 months) in 1L CIT cohort. The duration of 1L therapy period (active treatment period+no treatment period before starting 2L) was 17.4 months (SD 11.6 months; median 14.4 months) in 1L ibrutinib and 15.9 months (SD 12.1 months; median 13.0 months) in 1L CIT cohort. In the 1L ibrutinib versus 2L+ ibrutinib cohorts, the mean length of follow-up period was 16.7 months (SD 11.5 months; median 13.1 months) and 16.9 months (SD 10.5 months; median 14.8 months), respectively; the duration of 1L

FIGURE 2 Comparison of TTNT Between 1L Ibrutinib and 2L+ Ibrutinib

Patient at risk	6 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months
Ibrutinib 1L, n (%)	122 (81.9)	86 (57.7)	56 (37.6)	38 (25.5)	21 (14.1)	13 (8.7)	6 (4.0)	0 (0)
Ibrutinib 2L+, n (%)	104 (69.8)	73 (49.0)	46 (30.9)	24 (16.1)	12 (8.1)	3 (2.0)	2 (1.3)	0 (0)

^aHazard ratios were calculated using Cox proportional hazards regression models in the propensity score-matched cohorts.

1L=first line; 2L+=second line or later; CI=confidence interval; CIT=chemoimmunotherapy; HR=hazard ratio; TTNT=time to next treatment.

therapy period was 15.9 months (SD 11.9 months; median 12.9 months) in the 1L ibrutinib cohort and the duration on 2L/3L therapy period was 13.7 months (SD 10.1 months; median 11.6 months) in the 2L+ ibrutinib cohort.

TTNT in the Matched Cohorts

KM analysis of TTNT revealed that 1L ibrutinib patients had significantly longer TTNT than CIT 1L or ibrutinib 2L+ patients (log-rank $P<0.0001$; Figure 1 and Figure 2). Kaplan-Meier estimates at landmark time points were presented in Table 1. Median TTNT was not reached in the 1L ibrutinib cohort during the available follow-up. During the follow-up period, the hazard of initiating a new treatment was also lower for patients treated with 1L ibrutinib versus 1L CIT (48% lower) or ibrutinib 2L+ (61% lower; Figure 1 and Figure 2).

GLM-Adjusted All-Cause HRU and Costs PPPM in the Matched Cohorts

The 1L ibrutinib cohort had significantly lower all-cause HRU including inpatient (RR=0.38, 95% CI=0.28-0.52; $P\leq 0.05$)

and outpatient (RR=0.72, 95% CI=0.68-0.77; $P\leq 0.05$) visits PPPM, and shorter LOS PPPM (RR=0.46, 95% CI=0.32-0.67; $P\leq 0.05$) compared with the CIT 1L cohort (Figure 3). Compared with the CIT 1L cohort, the ibrutinib cohort had \$7,308 lower monthly all-cause medical costs (95% CI=−\$9,892 to −\$4,895; $P\leq 0.05$), mainly attributable to the lower monthly all-cause outpatient costs (−\$5,305; 95% CI=−\$7,563 to −\$3,397; $P\leq 0.05$) followed by the monthly all-cause inpatient costs (−\$1,243; 95% CI=−\$1,869 to −\$556; $P\leq 0.05$) (Figure 4). Monthly outpatient costs were driven mainly by the lower monthly costs related to the administration of antineoplastic agents (−\$3,201; 95% CI=−\$6,781 to −\$1,984; $P\leq 0.05$). Higher all-cause pharmacy costs in the ibrutinib cohort (\$5,204; 95% CI=\$4,875-\$5,489; $P\leq 0.05$) were offset by lower medical costs, resulting in overall net monthly all-cause total cost savings of \$2,160 (95% CI=−\$4,840-\$347; $P>0.05$); however, the difference was not statistically significant (Figure 4).

FIGURE 3 GLM-Adjusted All-Cause HRU and Health Care Costs PPPM in 1L Ibrutinib Versus 1L CIT Cohorts

Note: Risk ratio was obtained from negative binomial model in the matched cohorts, adjusting for baseline LOS and total costs; 95% CI and P values were obtained from a nonparametric bootstrap procedure.

^aAvoidable hospitalizations per AHRQ PQI included hospitalizations for asthma, bacterial pneumonia, chronic obstructive pulmonary disease, dehydration, diabetes, heart failure, hypertension, perforated appendix, or urinary tract infection.

^bSignificant at $P \leq 0.05$.

1L = first line; AHRQ = Agency for Healthcare Research and Quality; CI = confidence interval; CIT = chemoimmunotherapy; GLM = generalized linear model; HRU = health care resource utilization; LOS = length of stay; PPPM = per patient per month; PQI = prevention quality indicators.

Sensitivity Analysis

Similar trends were observed with the PSM adjusted for the index quarter, as well as the IPTW approach, showing that 1L ibrutinib had significantly longer TTNT compared with the CIT 1L (PSM $P < 0.0001$; IPTW $P < 0.0001$) and 2L+ ibrutinib cohorts (PSM $P = 0.0015$; IPTW $P = 0.0018$). Additionally, the 1L ibrutinib cohort had significantly lower HRU and all-cause total medical costs but similar all-cause total costs compared with the CIT 1L cohort.

Discussion

This claims-based study reveals insights into the real-world treatment outcomes including TTNT, HRU, and costs among CLL/SLL patients in the VHA population. The results of this study show that 1L ibrutinib is associated with a significantly longer TTNT than 1L CIT and 2L+ ibrutinib. These data continue to support, in a real-world setting, the superior efficacy of ibrutinib over CIT treatments in 1L as seen in ibrutinib clinical trials.^{11,18,20,30}

The most critical determinants of therapeutic options are the presence of del(17p)/TP53 mutation, physical fitness/age, and duration of previous response with earlier treatment.³¹ In CLL, which is diagnosed predominantly in an elderly population, the toxicities of therapy are of special concern. Toxicities can result in the interruption of therapy, diminish the opportunity for response, and can result in morbidity.

These adverse patient outcomes can result in increased HCRU and cost. However, treatment with ibrutinib has been well tolerated, and the most common adverse events have generally been low grade and transient.²⁵

Consistent with high rates of progression-free survival observed among ibrutinib patients in several clinical trials,^{11,15,17-20,32,33} it was observed that 73.7% and 65.4% of the patients who initiated ibrutinib single-agent in 1L did not initiate a new treatment after 24 and 36 months of follow-up, respectively. It is acknowledged, however, that only 25% of our population was evaluated after 24 months and only 10% after 36 months of follow-up due to censoring events. For indolent disease such as CLL, longer TTNT may provide a meaningful endpoint for patients and is therefore an important outcome measure.³⁴

Our findings align with the results of a previous real-world study that showed that ibrutinib had a longer TTNT versus CIT in 1L; however, the percentage of patients on ibrutinib in 1L remaining on the same treatment was higher in the previous study ($\approx 89\%$) at 24 months of follow-up.²⁴ Possible explanations for the discrepancies could be difference in patient age, comorbidities, adherence, or study design. Nevertheless, both studies provided real-world evidence of the sustained progression-free survival benefits of ibrutinib over CIT in 1L.^{24,34}

Notably, our study is unique in having a longer follow-up; we observed that at 48 months of follow-up, the percentage of

FIGURE 4 GLM-Adjusted Health Care Costs PPPM in 1L Ibrutinib Versus 1L CIT Cohorts

Note: Mean difference was calculated as the difference in the mean estimates obtained from GLM using gamma distribution and log link performed in the matched cohorts, adjusting for baseline LOS and total costs; 95% CI and P values were obtained from a nonparametric bootstrap procedure.

^aAvoidable hospitalizations per AHRQ PQI included hospitalizations for asthma, bacterial pneumonia, chronic obstructive pulmonary disease, dehydration, diabetes, heart failure, hypertension, perforated appendix, or urinary tract infection.

^bAll-cause total medical costs include inpatient and outpatient costs.

^cSignificant at $P \leq 0.05$.

1L = first line; AHRQ = Agency for Healthcare Research and Quality; CI = confidence interval; CIT = chemoimmunotherapy; GLM = generalized linear model; HRU = health care resource utilization; LOS = length of stay; PPPM = per patient per month; PQI = prevention quality indicators.

the 1L ibrutinib cohort remaining free from needing a next-line treatment was only 8% lower than at 24 months, and, in the 1L CIT cohort, twice the number of patients remained free from needing a next-line treatment at 48 months. We also found that patients who initiated ibrutinib in 1L had significantly longer TTNT than patients with ibrutinib in 2L/3L, which suggests the potential benefit of early treatment with ibrutinib.

Consistent with the previous real-world study by Emond et al. (2019),²⁴ the current study results show that 1L ibrutinib was associated with lower all-cause HRU and medical costs compared with 1L CIT. The total medical costs incurred by 1L ibrutinib patients in the current study were approximately 68% lower than in the CIT 1L cohort. Additionally, we observed that the estimates of total cost reduction in the ibrutinib cohort in 1L support conclusions made by previous studies that found a significant difference in HRU and total costs between 1L ibrutinib and 1L CIT.^{24,36-39} Although the all-cause medical costs completely offset the pharmacy costs in the 1L ibrutinib cohort, no statistical significance was observed in the all-cause total costs between 1L ibrutinib and 1L CIT cohorts.

Limitations

The findings from our study should be viewed in the context of some study limitations. The presence of a claim for a filled prescription does not indicate that the medication was consumed or taken as prescribed. The presence of a diagnosis code on a medical claim does not necessarily indicate a positive presence of disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather indicating the actual presence of the disease; however, we sought to mitigate this by requiring ≥ 2 diagnosis codes for CLL or SLL. Another limitation of claims data is that disease progression is not directly available. The most accepted approach used in cancer studies with claims data is to have TTNT act as a proxy for progression, although patients may start next treatment due to reasons other than progression, for example, intolerability.^{6,7,25,27,38,40-42}

Certain information that could influence study outcomes, such as clinical and disease-specific parameters, is not readily available in claims data. Also, there may be residual confounders due to unobserved or unrecorded clinical characteristics, as observed in any other claims-based study. It is recognized that the baseline clinical conditions are based on presence of specific diagnosis codes in the claims and the clinical

presentations may be underreported. Ibrutinib was approved in 2014 for the 1L treatment of CLL/SLL patients; any 1L use before that time is either off-label or (likely) a misclassification of patients as new users due to the limited pre-index data available in the data source.

Additionally, it is important to note that del(17p)/TP53 mutation information for each patient is not available in VA claims. Also, the information of fluorescent in situ hybridization (FISH) testing was not extracted from the data, as evaluating the frequency of FISH testing was not a part of the study objectives. It has been shown that ibrutinib works well in treatment of CLL patients with del(17p)/TP53 mutation whereas CIT does not. Therefore, the differences in outcomes between the subgroup of ibrutinib versus CIT patients with del(17p)/TP53 mutation would likely be even more prominent than the results presented in this study.^{11,41,42}

Also, resource utilization information on HRU might not be complete if Medicare-eligible veterans use health care services outside the VA system. However, the VA provides more comprehensive prescription drug coverage than Medicare, so patients have a strong financial incentive to receive pharmacotherapy from VA providers.

Additionally, generalizability of the findings may be limited, as the current analysis was conducted with VHA data, which is a population with more comorbidities, with more limited access to care than the general population, and is predominantly composed of male patients with previous military service.

Finally, retrospective analysis of real-world use of therapies cannot eliminate selection bias. Physicians prescribe medications to patients who they think would benefit the most from the selected treatments, based on their clinical judgment, appetite for adopting innovation, and patient clinical characteristics. However, with proper adjustment of observable data elements and acknowledgement of potential limitations, real-world data can still provide meaningful insights from routine clinical practice.

Conclusions

The findings of our study show that newly diagnosed patients with CLL/SLL who initiated 1L treatment with once-daily ibrutinib remained on treatment longer than those who initiated 1L CIT or those using ibrutinib in later lines. Additionally, patients who initiated 1L ibrutinib had lower HRU and medical costs as compared with those who initiated 1L CIT. Further research with larger sample sizes and longer follow-up periods is needed to understand the evolving treatment patterns and outcomes of ibrutinib with its increased utilization in the 1L for this predominantly older population with high unmet needs.

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DISCLOSURES

This research was sponsored by Janssen Scientific Affairs. The analyses were performed by STATinMED Research. Huang is an employee of Janssen Scientific Affairs and may own company stock. Sundaram was an employee of Janssen Scientific Affairs at the time this study was conducted. Borra and Janjan are employees of STATinMED Research, a paid consultant to the study sponsor. Wang, Li, and Shrestha were employees of STATinMED Research at the time this study was conducted.

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