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TREATMENT PATTERNS, ADVERSE EVENTS, AND ECONOMIC BURDEN IN A PRIVATELY INSURED POPULATION OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA IN THE UNITED STATES

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Introduction

- Treatment recommendations for patients with chronic lymphocytic leukemia (CLL) depend on the disease state, the presence or absence of genetic abnormalities, the patient's age and their general health.[1,2]
- Patients receiving treatment for CLL may experience a range of mild to severe adverse events (AEs) that can affect morbidity, lead to treatment changes and increase economic burden related to their management.
- Contemporary data describing treatment patterns, AEs and outcomes in clinical practice in patients with CLL are sparse.

Objective

- To assess treatment patterns, type of AEs, healthcare resource use (HCRU) and costs in patients with CLL.

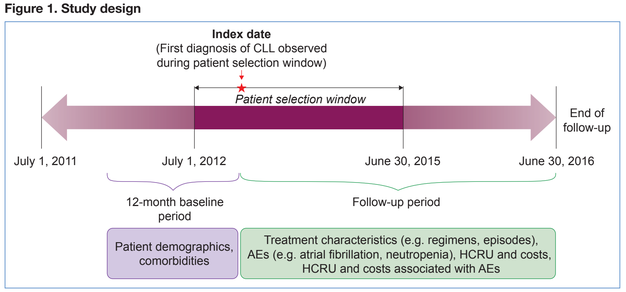
Methods

- In this retrospective cohort study, we used the Truven Health MarketScan® Research Databases containing administrative claims data for individuals enrolled in employer-sponsored private health insurance plans across the USA.
- These databases provide longitudinal data on medical and pharmacy service utilization, and associated payments for a nationally representative population of privately insured patients in the USA.
- Adult patients with CLL (based on diagnosis codes) were selected if they had continuous health plan enrollment for ≥ 12 months before the first CLL diagnosis (index date) without any evidence of any CLL-directed treatment.
- A summary of the study design is illustrated in Figure 1.
- Treatment patterns up to the fourth line of therapy (LOTs) and occurrence of AEs (identified using ICD-9/ICD-10 codes) during CLL-directed treatment were assessed. First LOT was defined using a Healthcare Common Procedure Coding System (HCPCS) identifying agent-specific systemic therapy, plus any pharmacy claims containing a national drug code or generic name for a systemic therapy. Therefore, only patients receiving an identifiable systemic therapy were included in the analysis.
- Mean per-patient per-month HCRU and costs (in 2016 US dollars) were assessed overall and by number of unique AEs.
- Descriptive analyses are reported for all study measures. Multivariate Cox regression models were developed to estimate the risk of atrial fibrillation (A-fib) and bleeding in the first line among patients treated with a first-line systemic therapy, based on the time to first occurrence of A-fib or bleeding from the start of therapy in the population from the databases.

Results

- The characteristics of the patients meeting the eligibility criteria (n = 7639), including the Charlson comorbidity index score, were assessed at index or during the 12-month baseline period (Table 1).

Figure 1. Study design



AE, adverse event; CLL, chronic lymphocytic leukemia; HCRU, healthcare resource use.

Treatment patterns

- In total, 29% (n = 2211) of all patients received at least one treatment for CLL; the most common treatment categories, irrespective of LOT, were chemotherapy with or without immunotherapy (68%) and biologic therapy/immunomodulators (50%).
- Among patients receiving any CLL-directed treatment, 1379 (62%) received systemic therapy which could be classified as first-line (including use of hematopoietic stem cell transplantation administered with chemotherapy), while others received other treatments (autologous stem cell transplant: 0.1%, allogenic stem cell transplant: 0.5%, and radiation therapy: 12.6%).
- Of those receiving first-line systemic therapy, 26% (n = 355) went on to receive LOT-2, 30% (n = 106) received LOT-3, and 33% (n = 35) received LOT-4, during follow-up.
- The most common systemic therapy regimens, regardless of LOT, were bendamustine/rituximab (BR) (32%), rituximab monotherapy (24% [including maintenance]), ibrutinib monotherapy (15%) and fludarabine/cyclophosphamide/rituximab (FCR) (14%).
- Of these, BR was the most common LOT-1 regimen (28.1%), while ibrutinib monotherapy was the most common regimen in LOT-2 (20.8%) and in LOT-3 (25.5%).
- The use of idelalisib was limited to 1.6% of all patients receiving systemic therapy; however, an increasing trend was observed as patients moved from first to fourth LOT (< 1% in LOT-1, 3.1% in LOT-2, 4.7% in LOT-3, and 8.6% in LOT-4).

Table 1. Baseline characteristics of patients with CLL

All patients, N (%)	7639 (100.0%)
Age at index, years	
Mean (SD)	67.6 (12.7)
Median (Q1, Q3)	66 (59, 78)
Health plan type, n (%)	
HMO	776 (10.2%)
PPO	3972 (52.0%)
POS	434 (5.7%)
Other	2310 (30.2%)
Unknown	147 (1.9%)
Year of study index date (first diagnosis), n (%)	
2012	1825[e] (23.9%)
2013	2635 (34.5%)
2014	2281 (29.9%)
2015	898 (11.8%)
Length of follow-up (months)[a]	
Mean (SD)	22.0 (12.8)
Median	20.6
Minimum, Maximum	0.1, 47.9
Atrial fibrillation risk status,[b] n (%)	
High risk	3565 (46.7%)
Low risk	4074 (53.3%)
CCI score	
Mean (SD)	2.1 (2.3)
Median (Q1, Q3)	1 (0, 3)
Minimum, Maximum	0, 15
Daily pill burden[c]	
Mean (SD)	2.5 (2.8)
Median (Q1, Q3)	2 (0, 4)
Minimum, Maximum	0, 27
Average monthly costs[d]	
Mean (SD)	$962 ($2980)
Median (Q1, Q3)	$325 ($135, $752)
Minimum, Maximum	$0, $103 582

Note: all costs are in 2016 US dollars.
[a]Follow-up time was calculated as the number of days between the study index date and the end of the follow-up divided by 30.5.
[b]Atrial fibrillation risk status was defined based on the method used by Chyou *et al.* 2015.[3]
[c]Mean number of oral medications available in hand, on a daily basis, during the 30-day period before the study index date.
[d]Mean monthly all-cause costs over the 12-month baseline period (includes costs for inpatient stays, emergency department visits, office visits, other outpatient and ancillary care, and pharmacy visits) as incurred by health plans.
[e]Indicates data for partial year: for 2012, data include diagnoses from July through December, and for 2015, data include diagnoses from January through June.
CCI, Charlson comorbidity index; CLL, chronic lymphocytic leukemia; HMO, health maintenance organization; Q, quartile; POS, point of service; PPO, preferred provider organization; SD, standard deviation.

Adverse events

- The most common AEs identified in patients receiving one of the four most frequently prescribed treatments for CLL are presented by treatment regimen in Table 2.
- Based on multivariable Cox regression models, patients in the older age group (> 65 years), patients with a high baseline risk of A-fib and those treated with ibrutinib monotherapy had a significantly higher rate of A-fib during LOT-1 (Table 3). Treatment with ibrutinib in LOT-1 was a significant predictor of risk of hemorrhage/bleeding.

Table 2. Adverse events identified during treatment for CLL

	BR (n = 446)	FCR (n = 194)	Rituximab monotherapy (n = 327)	Ibrutinib monotherapy (n = 201)
Hematologic adverse events, %				
Anemia	35	32	37	35
Thrombocytopenia	16	17	19	20
Neutropenia	58	72	6	12
Nonhematologic adverse events, %				
Atrial fibrillation[a]	2	3	3	11
Dehydration	15	15	7	8
Dyspnea	28	24	19	25
Fatigue/asthenia	18	18	10	12
Fever/pyrexia	17	13	6	12
Hemorrhage/bleeding	7	7	9	13
Hypertension[a]	2	2	3	13
Infection	36	21	28	38
Nausea/vomiting	32	34	13	6
Pneumonia	7	6	8	12

Note: data reported for the most common AEs (≥ 10% in at least one of the columns).
[a]Baseline history of the adverse event precluded patients from being considered at risk for that adverse event during the follow-up period.
BR, bendamustine/rituximab; CLL, chronic lymphocytic leukemia; FCR, fludarabine/cyclophosphamide/rituximab.

Table 3. Multivariable Cox regression models assessing risk of atrial fibrillation and bleeding/ hemorrhage among patients treated with first-line therapy

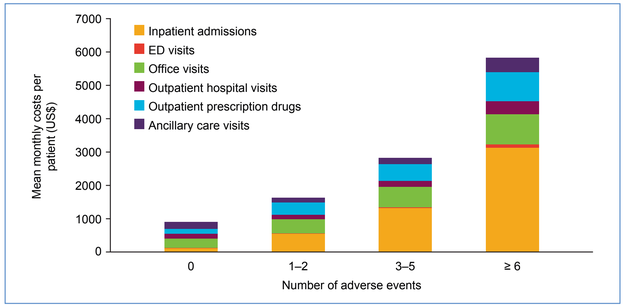
Covariates	Atrial fibrillation			Bleeding/hemorrhage		
	HR	95% CI		HR	95% CI	
Age at index (ref = 18–64 years)						
65+ years	**2.47**	**1.32**	**4.60**	1.32	0.81	2.16
Sex (ref = Male)						
Female	**0.59**	**0.38**	**0.90**	0.81	0.55	1.20
Year of index diagnosis (ref = 2012–2013)						
2014–2015	1.02	0.69	1.51	0.82	0.55	1.21
Health plan type (ref = HMO)						
Comprehensive	1.08	0.71	1.64	0.82	0.55	1.22
Others	1.16	0.55	2.03	**0.44**	**0.22**	**0.89**
CCI score (ref = 0)						
1	0.74	0.28	1.90	1.33	0.73	2.41
2	0.68	0.24	1.92	0.93	0.44	1.97
≥ 3	1.13	0.43	2.99	1.29	0.67	2.48
Atrial fibrillation risk status at baseline (ref = low risk)						
High risk	**5.72**	**2.53**	**12.96**	1.30	0.75	2.25
Other baseline risk factors						
Infection	0.72	0.47	1.10	1.20	0.81	1.78
Anemia	0.97	0.63	1.50	1.01	0.65	1.59
Neutropenia	0.64	0.20	2.08	1.56	0.66	3.73
Hemorrhage	0.96	0.59	1.57	1.22	0.76	1.97
Pneumonia	**2.07**	**1.15**	**3.76**	0.91	0.44	1.87
Thrombocytopenia	1.51	0.89	2.56	1.14	0.64	2.06
First-line treatment regimen (ref = BR)						
FCR	1.66	0.75	3.67	1.44	0.74	2.81
Ibrutinib monotherapy	**3.19**	**1.68**	**6.08**	**2.05**	**1.07**	**3.92**
Other regimens	1.42	0.83	2.45	1.58	0.96	2.61
Rituximab monotherapy	1.75	1.00	3.05	1.35	0.75	2.43

Note: HR estimates reported in bold style indicate that the 95% CIs do not include 1.
BR, bendamustine/rituximab; CCI, Charlson comorbidity index; CI, confidence interval; FCR, fludarabine/cyclophosphamide/rituximab; HMO, health maintenance organization; HR, hazard ratio.

Resource use and cost

- The mean monthly all-cause cost during the baseline period was $962 (standard deviation [SD] $2980).
- The mean monthly all-cause and CLL-related costs among patients **treated** with a systemic therapy were $7943 (SD, $15 757) and $5185 (SD, $9935), respectively.
- The mean monthly all-cause costs during the post-index date follow-up were $905 ($1865) among those with no AEs, $1655 ($5364) among those with 1–2 AEs, $2883 ($8483) among those with 3–5 AEs, and $6032 ($13 290) among those with ≥ 6 AEs (Figure 2).

Figure 2. All-cause monthly healthcare costs by practice setting and number of adverse events



ED, emergency department.

Conclusions

- This population-based study yielded recent real world evidence on treatment patterns, AEs, HCRU and costs in patients enrolled in commercial health plans in the USA.
- Among patients with CLL initiating treatment, immunochemotherapy, particularly BR, was the most common first observed therapy for CLL, while ibrutinib was the most common observed second- and third-line therapies.
- This study demonstrates that the AE burden associated with current treatments for CLL is substantial, and the management of treatment-related AEs may have a significant effect on overall healthcare costs.

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