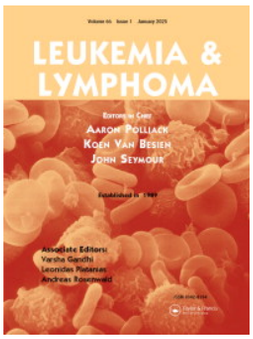

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Real-world outcomes following ibrutinib dose reduction in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma

Mazyar Shadman[a], Monika Salkar[b], Bhavini Srivastava[b], Sudeep Karve[b], Bruno Emond[c], Priyanka Gogna[c], Ameur M. Manceur[c], Marie-Hélène Lafeuille[c], Andrew Rava[d], Haiyan Sun[d], Amanda Howarth[d], Samantha Tomicki[d], Barnabie Agatep[e], Barton Jones[e], Erin Franceschini[b], Chadi Saifan[b], Shaffee Bacchus[b], Lindsey Roeker[f] and Deborah M. Stephens[g]

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ABSTRACT

This study used real-world data from three separate United States (US) databases to evaluate dosing patterns and time to next treatment (TTNT) following the first-incident adverse event (AE) in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) treated with first-line ibrutinib with and without dose reduction (DR). Median TTNT or death in patients with and without a DR following an AE in each database was as follows: Optum Clinformatics Data Mart (CDM): 59.5 and 30.6 months; ConcertAI: 27.1 and 18.0 months; and Medicare Fee-for-Service (FFS): 49.8 and 22.0 months, respectively. Median TTNT or death in patients with cardiac AEs, with and without a DR, was: Optum CDM: 44.4 and 22.9 months; ConcertAI: 29.9 and 18.3 months; and Medicare FFS: 49.6 and 14.0 months, respectively. Ibrutinib DR was associated with fewer outpatient visits and lower CLL/SLL-related medical costs. These findings suggest that utilizing ibrutinib DR may effectively manage tolerability without compromising clinical efficacy.

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KEYWORDS
Chronic lymphocytic leukemia; ibrutinib; real-world evidence; dose reduction

Introduction

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is the most common type of leukemia among older adults in the United States (US) [1,2]. Over the last decade, treatment options and outcomes for patients with CLL/SLL have been transformed with the introduction of targeted agents like Bruton tyrosine kinase inhibitors (BTKis) [3]. In 2014, ibrutinib became the first BTKi to receive approval from the US Food and Drug Administration (FDA) [4] and has shown significant progression-free survival and overall survival benefit in several randomized phase 3 trials involving patients with previously untreated and relapsed/refractory CLL/SLL [5–9]. With the longest follow-up of any BTKi [10], one study demonstrated that continuous treatment with single-agent ibrutinib improved survival outcomes in patients with CLL/SLL compared with those who discontinued treatment [11]. Thus, maintaining patients on therapy, as appropriate, may maximize treatment benefit. Patients with CLL/SLL commonly discontinue treatment due to tolerability issues or adverse events (AEs) [12–17]. The available formulations of ibrutinib offer dose reduction (DR) strategies to manage AEs. In clinical trials, efficacy outcomes were similar among patients with DR and without DR [18,19], although real-world data on ibrutinib dosing patterns and the association between DR and outcomes remain scarce [20,21].

Therefore, this study aimed to describe dosing patterns, time to next treatment (TTNT), healthcare resource use (HRU), and costs in patients with CLL/SLL with or without ibrutinib DR following an AE using real-world data from three separate data sources.

Methods

Data sources

This retrospective real-world study was conducted using three databases: Optum Clinformatics Data Mart (CDM), ConcertAI, and Medicare Fee-for-Service (FFS)

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enrollment and claims. Here, we report results obtained from the above-mentioned data sources separately. Optum CDM is an administrative claims database that includes de-identified information about inpatient and outpatient medical claims, pharmacy claims, and estimated costs of medical services from recipients of commercial health insurance and Medicare Advantage. ConcertAI is a de-identified oncology database that aggregates patient-level data from claims and multiple electronic medical record (EMR) systems using standard variable coding algorithms. Medicare FFS data, collected by the Centers for Medicare and Medicaid Services (CMS), comprise administrative information derived from reimbursement records or the payment of bills for all Medicare FFS beneficiaries for medical encounters and prescription drug events.

Study design and population

A study schema illustrating the analysis conducted across all three databases is presented in Figure 1. Patient inclusion and exclusion criteria varied across the three databases and are detailed in Supplemental Table 1. Generally, patients from each database were included in the analysis if they were aged ≥18 years at index ibrutinib claim, were diagnosed with CLL/SLL (per International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 204.1, and ICD-10-CM codes C83.0 and C91.1), initiated first-line (1L) ibrutinib at a starting dose of 420 mg/day, had an incident AE following the initiation of 1L ibrutinib, had a ≥12-month baseline period prior to the initiation of 1L ibrutinib, and had ≥30 to ≥90 days of continuous eligibility following initiation of 1L ibrutinib. Patients were excluded if they experienced any of the following: received ≥1 claim for an antineoplastic agent during the 6- to 12-month prior to initiating 1L ibrutinib, received an antineoplastic agent or combination therapy within 28 days (Optum CDM and ConcertAI only) or 30 days (Medicare FFS only) of initiating ibrutinib, received second-line therapy within ≤30 days after index date, received hematopoietic stem cell transplant (ConcertAI only), participated in a clinical trial for an experimental therapy, received a CYP3A inhibitor while taking ibrutinib, or were diagnosed with other malignancies.

Study outcomes

Across the three databases, demographics, clinical characteristics, treatment patterns, and TTNT were described among patients with and without DRs following AE occurrence. Patients with DR were defined as those who had a DR from the ibrutinib starting dose (420 mg/day) following the first-incident AE. Patients without DR were defined as those who remained on the initial dose of ibrutinib 420 mg/day for the entire duration of 1L therapy. First-incident AEs were categorized into cardiac- and noncardiac-related groups per ibrutinib US prescribing information. Cardiac AEs included atrial fibrillation (cardiac arrhythmias), ischemic heart disease, heart failure, congestive heart failure (cardiac failure), hypertension, cardiomyopathy, and ventricular tachyarrhythmia (cardiac arrhythmias)

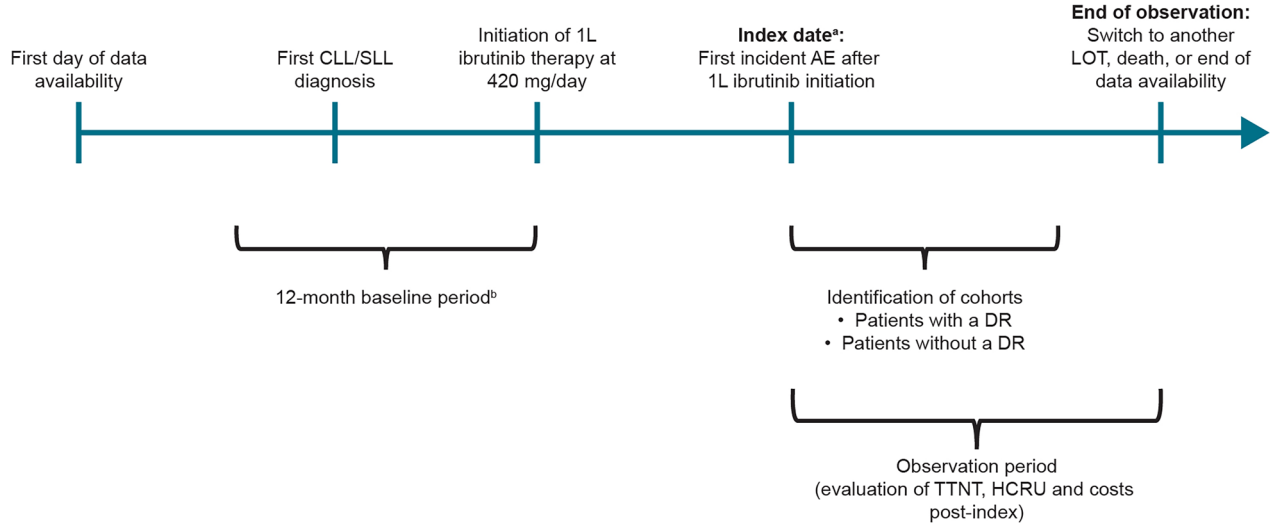

Figure 1. Study schema. 1L: first-line; AE: adverse event; CLL: chronic lymphocytic leukemia; DR: dose reduction; HCRU: healthcare resource utilization; LOT: line of therapy; SLL: small lymphocytic lymphoma; TTNT: time to next treatment. [a]Index date was defined as the first-incident AE after 1L ibrutinib initiation. [b]Baseline period was defined as 12 months prior to initiation of 1L ibrutinib (Optum CDM and Medicare FFS only) or to first-incident AE (ConcertAI only).

identified using ICD-9-CM/ICD-10-CM codes [4]. Noncardiac AEs included febrile neutropenia, anemia, neutropenia, pancytopenia, thrombocytopenia, diarrhea, abdominal pain, musculoskeletal pain, rash, respiratory infection (pneumonia), lymphopenia, and leukopenia identified using ICD-9-CM/ICD-10-CM codes [4]. TTNT was defined as the time from the first-incident AE to either the first dose of a next treatment (any non-ibrutinib therapy), a gap of >90 days between the last day of supply of ibrutinib and the date of the next ibrutinib claim (reinitiating with ibrutinib), or death. TTNT was evaluated for all patients (with any AE) and further stratified by those with cardiac and noncardiac AEs. Patients without a next treatment or who did not die were censored at the end of their continuous health insurance eligibility, at the earliest of activity, or at the end of data availability. All-cause and CLL/SLL-related comprehensive costs (patient plus payer perspectives) and HRU were evaluated from the first-incident AE to end of line of therapy (defined as a gap of >90 days in consecutive days supply of ibrutinib, next line of therapy, or death) and were reported per patient per month (PPPM). Costs were adjusted to 2021 US dollars (USD) using the medical care component of the Consumer Price Index (Optum CDM and Medicare FFS only).

Statistical analyses

Analyses were conducted separately for the three databases. Descriptive statistics were used to evaluate demographics and clinical characteristics, time to first-incident AE, TTNT, and HRU. TTNT was compared using Kaplan–Meier's analysis and adjusted time-varying Cox proportional hazards models among patients with and without DR. Multivariate models were adjusted for the following pre-index variables: year initiation of 1L ibrutinib, age, sex, geographic region, race, Charlson Comorbidity Index, diagnosis of renal failure (Optum CDM and Medicare FFS only), diagnosis of infection, any gastrointestinal condition or use of an antacid (Optum CDM and ConcertAI only), diagnosis of any DSM-V mental comorbidities (Optum CDM and ConcertAI only), diagnosis of musculoskeletal pain (including arthralgia) (Optum CDM and ConcertAI only), diagnosis of abdominal pain (Optum CDM and ConcertAI only), use of proton pump inhibitors, use of corticosteroids, time between first CLL/SLL diagnosis and start of 1L therapy, number of outpatient admissions, number of inpatient admissions, all-cause monthly healthcare costs (comprehensive perspective) (Optum CDM and Medicare FFS only), and diagnosis of fatigue/weakness (ConcertAI only). The models were also adjusted for the following time-varying covariates evaluated during each 30-day cycle post-index: cumulative number of incident AEs, all-cause monthly healthcare costs (comprehensive perspective) (Optum CDM and Medicare FFS only), and cumulative sum of inpatient admissions. All-cause, CLL/SLL-related HRU, and costs analyses (Optum CDM and Medicare FFS only) were reported during the follow-up period (from index date to the end of 1L ibrutinib). In the ConcertAI database, the HRU outcomes were measured between index date and end of 1L ibrutinib for all patients. *p* values were calculated using Chi-square tests for frequency data and *t*-tests for continuous data. This study is based on previously collected data from a commercially available database and does not contain any studies of human participants or animals performed by any of the authors.

Results

Patients

In the Optum CDM dataset, 658 patients with CLL/SLL treated with 1L ibrutinib who experienced an AE were identified. In this cohort, 95 patients (14%) had a DR and 563 patients (86%) did not have a DR following first-incident AE (Table 1; Supplemental Figure 1). Of the 522 patients identified from the ConcertAI database, 95 (18%) had a DR and 427 (82%) did not have a DR following first-incident AE (Table 1; Supplemental Figure 2). A total of 3575 patients were included in the Medicare FFS dataset; 459 patients (13%) had a DR and 3116 patients (87%) did not have a DR following first-incident AE (Table 1; Supplemental Figure 3). The mean (standard deviation (SD)) duration of 1L therapy was numerically longer in patients with a DR compared with those without DR following first-incident AE (Optum CDM: 922 [545] vs. 735 [517] days; ConcertAI: 548 [447] vs. 461 [434] days; Medicare FFS: 843 [595] vs. 562 [531] days) (Table 1). Mean (SD) time to first-incident AE in patients with or without a DR was as follows: Optum CDM, 161 (245) versus 227 (281) days; ConcertAI, 109 (156) versus 161 (254) days; Medicare FFS, 185 (245) versus 279 (341) days (Table 1). Mean (SD) time between first-incident AE and end of 1L therapy was numerically longer in patients with a DR compared with those without a DR (Optum CDM, 761 [498] vs. 508 [465] days; ConcertAI, 439 [383] vs. 300 [334] days; Medicare FFS 659 [528] vs. 284 [380] days) (Table 1).

Across all three datasets, baseline characteristics including age, sex, geographic region, and race were generally similar among patients with and without DR

Table 1. Duration of 1L therapy and time between first-incident AE and end of 1L therapy among patients with and without a DR: results from Optum CDM, ConcertAI, and Medicare FFS.

	Optum CDM		ConcertAI		Medicare FFS	
	Patients with DR, *n* = 95	Patients without DR, *n* = 563	Patients with DR, *n* = 95	Patients without DR, *n* = 427	Patients with DR, *n* = 459	Patients without DR, *n* = 3116
Duration of 1L therapy, mean ± SD [median], days	922 ± 545 [842]	735 ± 517 [606]	548 ± 447 [411]	461 ± 434 [313]	843 ± 595 [729]	562 ± 531 [393]
Time between first CLL/SLL diagnosis and treatment initiation, mean ± SD [median], days	998 ± 1059 [694]	761 ± 810 [530]	666 ± 574 [457]	707 ± 657 [520]	730 ± 552 [672]	747 ± 613 [636]
Time to the first-incident AE, mean ± SD [median], days	161 ± 245 [51]	227 ± 281 [119]	109 ± 156 [37]	161 ± 254 [65]	185 ± 245 [93]	279 ± 341 [143]
Time between first-incident AE and DR, mean ± SD [median], days	204 ± 245 [119]	NA	135 ± 178 [66]	NA	222 ± 271 [109]	NA
Time between first-incident AE and end of 1L therapy, mean ± SD [median], days	761 ± 498 [725]	508 ± 465 [352]	439 ± 383 [304]	300 ± 334 [185]	659 ± 528 [536]	284 ± 380 [114]

1L: first line; AE: adverse event; CDM: Clinformatics Data Mart; CLL: chronic lymphocytic leukemia; DR: dose reduction; FFS: Fee-for-Service; NA: not applicable; SD: standard deviation; SLL: small lymphocytic lymphoma.

Table 2. Baseline characteristics among patients with and without a DR: results from Optum CDM, ConcertAI, and Medicare FFS datasets.

	Optum CDM		ConcertAI		Medicare FFS[a]	
	Patients with DR, *n* = 95	Patients without DR, *n* = 563	Patients with DR, *n* = 95	Patients without DR, *n* = 427	Patients with DR, *n* = 459	Patients without DR, *n* = 3116
Age[b], mean ± SD [median], years	73.9 ± 9.5 [75.0]	72.1 ± 9.7 [73.0]	72.8 ± 9.6 [75.0]	69.7 ± 9.4 [69.0]	76.5 ± 7.5 [76.0]	75.6 ± 7.9 [76.0]
Sex, *n* (%)						
Women	38 (40)	206 (37)	39 (41)	158 (37)	195 (42)	1115 (36)
Men	57 (60)	357 (63)	56 (59)	269 (63)	264 (58)	2001 (64)
Geographic region, *n* (%)[b]						
Midwest	28 (30)	146 (26)	36 (38)	155 (37)	99 (22)	827 (27)
Northeast	17 (18)	64 (11)	12 (13)	34 (8)	114 (25)	702 (23)
South	31 (33)	196 (35)	32 (34)	172 (41)	159 (35)	1027 (33)
West	19 (20)	156 (28)	15 (16)	61 (14)	86 (19)	560 (18)
Unknown	0 (0)	1 (<1)	0 (0)	5 (1)	<11 (NA)	<11 (NA)
Race, *n* (%)						
White	77 (81)	418 (74)	70 (74)	316 (74)	409 (89)	2753 (88)
Black or African American	3 (3)	36 (6)	12 (13)	50 (12)	32 (7)	230 (7)
Asian	1 (1)	11 (2)	0 (0)	4 (1)	<11 (NA)	23 (1)
Other or unknown race	14 (15)	98 (17)	13 (14)	57 (13)	11 (2)	104 (3)
Year of 1L treatment initiation, *n* (%)						
2014–2016	11 (12)	80 (14)	16 (17)	79 (19)	169 (37)	1000 (32)
2017	20 (21)	77 (14)	16 (17)	64 (15)	89 (19)	548 (18)
2018	21 (22)	115 (20)	20 (21)	76 (18)	87 (19)	561 (18)
2019	23 (24)	146 (26)	20 (21)	83 (19)	73 (16)	695 (22)
2020	14 (15)	86 (15)	16 (17)	79 (19)	41 (9)	312 (10)
2021	6 (6)	59 (10)	6 (6)	40 (9)	<11 (NA)	<11 (NA)
2022	NA	NA	1 (1)	6 (1)	<11 (NA)	<11 (NA)
Time between DR and end of 1L, mean ± SD [median], days	556 ± 479 [408]	NA	303 ± 345 [202]	NA	439 ± 435 [280]	NA
CCI score, mean ± SD [median][c]	4 ± 2 [4]	4 ± 2 [3]	0.6 ± 1.0 [0.0]	0.5 ± 1.2 [0.0]	4.4 ± 2.6 [4.0]	4.5 ± 2.6 [4.0]

1L: first line; CCI: Charlson Comorbidity Index; CDM: Clinformatics Data Mart; DR: dose reduction; FFS: Fee-for-Service; NA: not applicable; SD: standard deviation.
[a]Cells based on <11 cases are masked per the CMS data suppression policy (Medicare FFS).
[b]Evaluated at initiation of 1L therapy (Optum CDM and ConcertAI).
[c]CCI scores were calculated using the 2011 version established by Quan et al. [22]. Malignancy in the CCI score calculation was not included as every patient had cancer (ConcertAI only).

(Table 2). The median age among patients with and without DR was as follows: Optum CDM, 75.0 versus 73.0 years; ConcertAI, 75.0 versus 69.0 years; Medicare FFS, 76.0 versus 76.0 years (Table 2).

Time to next treatment

With median follow-up of 32.9 months in patients with a DR and 27.0 months in patients without a DR following first-incident AE in the Optum CDM dataset,

median TTNT was 59.5 and 30.6 months, respectively (Figure 2(A)); the adjusted hazard ratio (HR) was 0.62 (95% CI 0.42–0.92; p = .017) for patients with a DR compared with those without a DR (Supplemental Figure 4). In the ConcertAI dataset, the median follow-up was 20.5 months in patients with a DR and 13.5 months in patients without a DR following first-incident AE, with median TTNT of 27.1 months and 18.0 months, respectively (Figure 2(B)); the adjusted HR was 0.71 (95% CI 0.53–0.96; p = .027) for patients with a DR compared with those without a DR (Supplemental Figure 4). Among the Medicare FFS dataset, median follow-up was 31.7 months in patients with a DR and 24.0 months in patients without a DR following first-incident AE, with median TTNT of 49.8 and 22.0 months, respectively (Figure 2(C)); the adjusted HR was 0.89 (95% CI 0.71–1.12; p = .330) (Supplemental Figure 4).

In patients with cardiac AEs, with and without DR, the median TTNT or death was 44.4 and 22.9 months (adjusted HR 0.74; 95% CI, 0.38–1.44; p = .374), respectively, in the Optum CDM dataset (Supplemental Figure 5(A)); 29.9 and 18.3 months (adjusted HR 0.69; 95% CI, 0.45–1.04; p = .077), respectively, in the ConcertAI dataset (Supplemental Figure 6(A)); and 49.6 and 14.0 months (adjusted HR 0.90; 95% CI, 0.71–1.13; p = .36), respectively, in the Medicare FFS dataset (Supplemental Figure 7(A)). Among patients with noncardiac AEs, with and without DR, the median TTNT was 59.5 months and not reached (adjusted HR 0.45; 95% CI, 0.24–0.85; p = .013), respectively, in the Optum CDM dataset (Supplemental Figure 5(B)); 24.9 and 18.0 months (adjusted HR 0.73; 95% CI, 0.46–1.17; p = .190), respectively, in the ConcertAI dataset (Supplemental Figure 6(B)); and 53.0 and 24.7 months (adjusted HR 0.91; 95% CI, 0.73–1.15; p = .45), respectively, in the Medicare FFS dataset (Supplemental Figure 7(B)).

Healthcare utilization and direct costs

During follow-up, the mean PPPM all-cause inpatient hospital admissions in patients with and without a DR were: Optum CDM, 0.05 versus 0.14, p < .001; ConcertAI, 0.52 versus 0.54, p = .893; and Medicare FFS, 0.04 versus 0.04, p < .001. The mean number of all-cause outpatient visits was: Optum CDM, 2.71 versus 2.87, p = .457; ConcertAI, 0.31 versus 0.45, p = .027; and Medicare FFS, 0.81 versus 0.80, p < .001. The mean number of all-cause emergency department visits was: Optum CDM, 0.10 versus 0.22, p = .043; ConcertAI, 0.03 versus 0.05, p = .298; and Medicare FFS, 0.07 versus 0.07, p < .001 (Table 3).

In the CLL/SLL-related HRU PPPM, the mean number of inpatient hospital admission in patients with and without a DR was: Optum CDM, 0.04 versus 0.09, p < .001; ConcertAI, 0.16 versus 0.15, p = .752; and Medicare FFS, 0.03 versus 0.03, p < .001. The mean number of outpatient visits was: Optum CDM, 1.14 versus 1.33, p = .237; ConcertAI, 0.06 versus 0.07, p = .627; and Medicare FFS, 0.37 versus 0.40, p < .001. Patients with a DR had significantly lower mean CLL/SLL-related medical costs PPPM during the entire follow-up period compared with patients without a DR (Optum CDM, $2335 vs. $6884, p < .001; Medicare FFS, $1127 vs. $1303 p < .001) (Table 4).

Discussion

This study provides real-world evidence from three US databases regarding treatment patterns, HRU, and costs for patients with CLL/SLL who experienced an ibrutinib DR following an AE. Our findings demonstrated that mean time between ibrutinib initiation and end of 1L treatment was numerically longer in patients with a DR compared with those without a DR. Moreover, ibrutinib DR was associated with numerically longer TTNT in patients with cardiac AEs. Additionally, in the Optum CDM and ConcertAI databases, patients who underwent a DR had fewer outpatient hospital visits PPPM compared with those without a DR.

Collectively, these findings suggest that ibrutinib DR following an AE (cardiac or noncardiac AE) can be an effective strategy to maintain patients on treatment longer. In patients with CLL/SLL, BTKis, whether used as single agents or in combination with anti-CD20 antibodies, are prescribed until disease progression or intolerance occurs [9,23]. However, many patients experience tolerability issues with BTKi treatments, leading to treatment discontinuation [24]. Discontinuations due to ibrutinib intolerance might be preventable through DR to manage AEs.

Although newer BTKis are available, implementing ibrutinib DR appropriately instead of prematurely switching to a different BTKi can help manage tolerability issues without compromising efficacy [10,21,25]. This approach is particularly beneficial given that cardiac AEs are a class effect of BTKis. Therefore, DR with ibrutinib could be an effective strategy to maintain long-term treatment in patients with cardiac comorbidities. The impact of ibrutinib DR was demonstrated

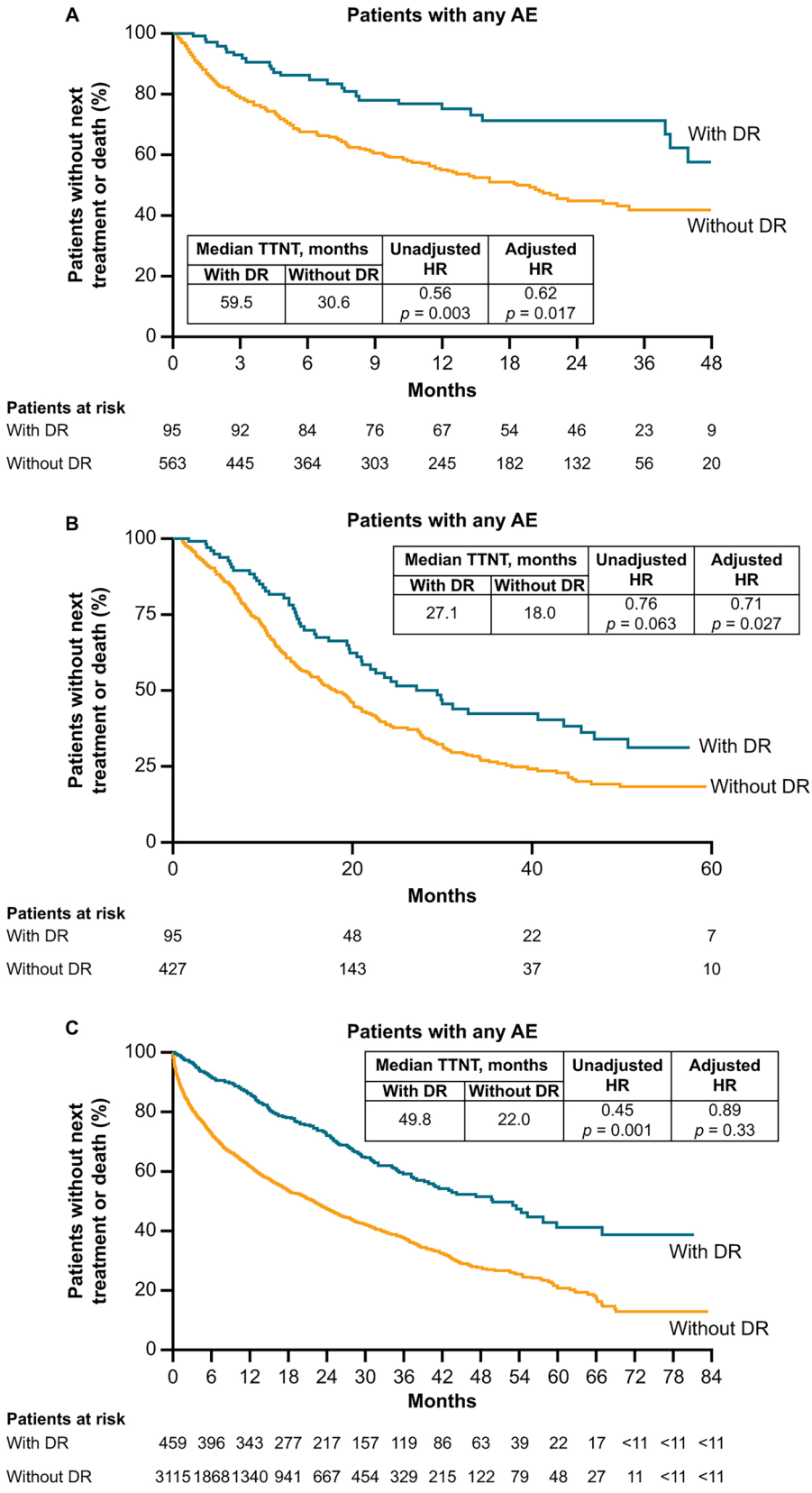

Figure 2. TTNT among patients with and without a DR: results from (A) Optum CDM, (B) ConcertAI[a], and (C) Medicare FFS[b] datasets. AE: adverse event; CDM: Clinformatics Data Mart; DR: dose reduction; FFS: Fee-for-Service; HR: hazard ratio; TTNT: time to next treatment. [a]Patient follow-up time was cut to a maximum of 60 months. [b]Data based on <11 cases are masked per the CMS data suppression policy.

Table 3. Healthcare resource utilization among patients with and without a DR: results from Optum CDM, ConcertAI, and Medicare FFS datasets.

	Optum CDM			ConcertAI			Medicare FFS		
	Patients with DR, *n* = 95	Patients without DR, *n* = 563	*p* value	Patients with DR, *n* = 95	Patients without DR, *n* = 427	*p* value	Patients with DR, *n* = 459	Patients without DR, *n* = 3116	*p* value
Duration of time from first-incident AE to end of line of therapy, mean ± SD [median], months	25.4 ± 16.6 [24.2]	17.0 ± 15.5 [11.8]	<.001*	14.4 ± 12.6 [9.99]	9.9 ± 10.97 [6.1]	<.001*	28.1 ± 19.8 [24.3]	18.7 ± 17.7 [13.1]	<.001*
All-cause HRU PPPM, mean ± SD [median]									
Number of outpatient visits	2.71 ± 1.68 [2.43]	2.87 ± 3.24 [2.08]	.457	0.31 ± 0.49 [0.10]	0.45 ± 0.87 [0.12]	.027	0.81 ± 0.85 [0.65]	0.80 ± 0.85 [0.59]	<.001*
Number of inpatient admissions	0.05 ± 0.10 [0.00]	0.14 ± 0.41 [0.00]	<.001*	0.52 ± 1.29 [0.02]	0.54 ± 1.26 [0.00]	.893	0.04 ± 0.08 [0.00]	0.04 ± 0.19 [0.00]	<.001*
Number of ED visits	0.10 ± 0.15 [0.04]	0.22 ± 1.41 [0.00]	.043*	0.03 ± 0.12 [0.00]	0.05 ± 0.18 [0.00]	.298	0.07 ± 0.12 [0.04]	0.07 ± 0.22 [0.00]	<.001*
Number of visits for other services[a]	0.58 ± 0.68 [0.34]	0.73 ± 1.70 [0.37]	.153	0.82 ± 0.97 [0.58]	0.70 ± 0.98 [0.31]	.278	0.32 ± 0.52 [0.00]	0.31 ± 0.55 [0.00]	<.001*
CLL/SLL-related HRU[b] PPPM, mean ± SD [median]									
Number of outpatient visits	1.14 ± 1.13 [0.95]	1.33 ± 2.43 [0.76]	.237	0.06 ± 0.17 [0.00]	0.07 ± 0.21 [0.00]	.627	0.40 ± 0.48 [0.28]	0.37 ± 0.50 [0.23]	<.001*
Number of inpatient admissions	0.04 ± 0.08 [0.00]	0.09 ± 0.29 [0.00]	<.001*	0.16 ± 0.46 [0.00]	0.15 ± 0.53 [0.00]	.752	0.03 ± 0.07 [0.00]	0.03 ± 0.16 [0.00]	<.001*
Number of ED visits	0.03 ± 0.09 [0.00]	0.04 ± 0.30 [0.00]	.398	0.00 ± 0.00 [0.00]	0.00 ± 0.02 [0.00]	.167	0.02 ± 0.05 [0.00]	0.02 ± 0.11 [0.00]	<.001*
Number of visits for other services[a]	0.20 ± 0.35 [0.04]	0.24 ± 0.66 [0.00]	.333	0.08 ± 0.34 [0.00]	0.03 ± 0.12 [0.00]	.160	0.32 ± 0.52 [0.10]	0.06 ± 0.22 [0.00]	<.001*

*$p \leq .05$.
AE: adverse event; CDM: Clinformatics Data Mart; CLL: chronic lymphocytic leukemia; DR: dose reduction; ED: emergency department; FFS: Fee-for-Service; HRU; health resource utilization; PPPM: per patient per month; SD: standard deviation; SLL: small lymphocytic lymphoma.
[a]Other services include durable medical equipment and dental and vision care.
[b]CLL-related HRU and medical costs were defined as the subset of claims and costs for claims with a diagnosis for CLL in any position. CLL-related pharmacy costs were defined as costs for claims for agents used in the treatment of CLL.

Table 4. All-cause and CLL/SLL-related costs among patients with and without a DR: results from Optum CDM and Medicare FFS datasets[a].

	Optum CDM			Medicare FFS		
	Patients with DR, *n* = 95	Patients without DR, *n* = 563	*p* value	Patients with DR, *n* = 459	Patients without DR, *n* = 3116	*p* value
Costs PPPM, mean ± SD [median]						
All-cause costs, 2021 USD						
Total	14,558 ± 6236 [14,602]	19,992 ± 29,150 [15,076]	<.001*	12,657 ± 4248 [12,491]	15,348 ± 6008 [14,747]	<.001*
Medical	3960 ± 5800 [1822]	10,592 ± 29,072 [2325]	<.001*	2121 ± 3251 [1235]	2383 ± 6157 [980]	<.001*
Outpatient	1848 ± 2348 [983]	2778 ± 11,820 [858]	.093	518 ± 1826 [193]	510 ± 1229 [165]	<.001*
Inpatient	1878 ± 4316 [0]	7174 ± 25,983 [0]	<.001*	618 ± 1659 [0]	833 ± 4849 [0]	<.001*
ED	152 ± 265 [33]	431 ± 3325 [0]	.051	52 ± 96 [19]	61 ± 255 [0]	<.001*
Other services[b]	82 ± 145 [28]	210 ± 1228 [26]	.018*	710 ± 1227 [358]	785 ± 2231 [275]	<.001*
Pharmacy	10,598 ± 3883 [11,945]	9400 ± 5921 [12,510]	.012*	10,536 ± 3042 [10,411]	12,965 ± 2571 [13,226]	<.001*
CLL/SLL-related costs[c], 2021 USD						
Total	12,698 ± 5124 [13,071]	16,006 ± 23,594 [14,028]	.003*	11,395 ± 3717 [11,273]	13,933 ± 4873 [13,790]	<.001*
Medical	2335 ± 4167 [644]	6884 ± 23,260 [924]	<.001*	1127 ± 2476 [380]	1303 ± 4858 [294]	<.001*
Outpatient	766 ± 1626 [335]	1185 ± 4786 [217]	.111	302 ± 1550 [70]	279 ± 950 [51]	<.001*
Inpatient	1492 ± 3659 [0]	5540 ± 22,675 [0]	<.001*	507 ± 1405 [0]	666 ± 4320 [0]	<.001*
ED	60 ± 186 [0]	125 ± 1092 [0]	.188	22 ± 66 [19]	24 ± 176 [0]	<.001*
Other services[b]	17 ± 43 [2]	34 ± 185 [0]	.058	211 ± 741 [43]	255 ± 1288 [29]	<.001*
Pharmacy	10,363 ± 3831 [11,624]	9122 ± 5928 [12,144]	.008*	10,268 ± 3005 [10,195]	12,630 ± 2342 [12,986]	<.001*

CDM: Clinformatics Data Mart; CLL: chronic lymphocytic leukemia; DR: dose reduction; ED: emergency department; FFS: Fee-for-Service; PPPM: per patient per month; SLL: small lymphocytic lymphoma; USD: United States dollar.
*$p \leq .05$.
[a]Due to data limitations, costs were not evaluated for the ConcertAI database.
[b]Other services included durable medical equipment and dental and vision care.
[c]CLL-related medical costs were defined as the subset of claims and costs for claims with a diagnosis for CLL in any position. CLL-related pharmacy costs were defined as costs for claims for agents used in the treatment of CLL.

in the RESONATE-2 clinical trial wherein active management of AEs with ibrutinib DR was associated with AE resolution in most patients [10]. Similarly, a real-world study of patients with CLL/SLL treated with 1L ibrutinib showed higher adherence rates in those who had dose adjustments compared with those who did not [21]. Pooled analyses of clinical trial data further indicated that dose modifications for cardiac AEs might enable patients to continue benefiting from long-term ibrutinib use and reduce the risk of recurrent cardiac AEs [25].

Additionally, dose modifications of 1L ibrutinib were not associated with an increased risk of initiating subsequent treatment in patients with CLL/SLL, including those at high risk for cardiovascular events [26,27]. The National Comprehensive Cancer Network (NCCN) guidelines recently highlighted that ibrutinib dose modifications can resolve intolerance issues without compromising efficacy [28]. The analyses of the Optum CDM and ConcertAI datasets showed that ibrutinib DR was associated with fewer CLL/SLL-related outpatient visits and lower medical costs for Optum CDM and Medicare datasets. These results underscore the importance of dose adjustment strategies in maximizing time on treatment and potentially reducing HRU and costs for patients with CLL/SLL.

This study had several limitations. Determination of an AE is based on presence of a medical record with relevant ICD-9-CM or ICD-10-CM codes; thus, causal association between an AE and subsequent DR cannot be inferred from the claims databases. Incident AEs were identified following treatment initiation and may not be related to treatment use. Additionally, reasons for DR were not available in the databases, and the grading of AEs is not documented in claims databases. Omissions and inaccuracies are inherent in claims/EMR data; administrative closed claims databases are designed for provider billing and reimbursement and do not capture complete medical history or physician notes. This may contribute to potential misclassification of AEs, baseline comorbidities, and outcomes. However, any inaccuracies would likely affect all cohorts equally and, thus, should have had no impact on conclusions. Furthermore, a claim/prescription for a medication did not necessarily indicate its use. Finally, as DR occurred post–index date, patients with a DR may have been subject to immortal time bias. Time-varying Cox proportional hazard models were used to mitigate potential bias introduced by this method. Multivariable model adjustment may have been subject to residual confounding due to unmeasured confounders.

In conclusion, optimizing time on treatment without disease progression is crucial in oncology and, in this case, CLL/SLL. Our findings, resulting from real-world data from three US claims databases, support ibrutinib DR as an effective AE management strategy. This approach could help patients remain on treatment longer while maximizing clinical benefit and potentially reducing healthcare costs.

Author contributions

MShadman and MSalkar: conceptualization, interpretation of findings, writing – original draft, writing – review, and editing; BE, PG, AMM, M-HL, AH, AR, ST, HS, BA, and BJ: methodology, formal analysis, interpretation of findings, project management, visualization, writing – review, and editing. All authors participated in the writing and review of the manuscript.

Disclosure statement

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Data availability statement

The datasets generated and/or analyzed during the current study are not publicly available due to the data use agreements with the vendors associated with the Optum Clinformatics Data Mart (CDM), ConcertAI, and Medicare Fee-for-Service (FFS) databases. The data are available through requests made directly to Optum CDM, ConcertAI, and Medicare FFS, subject to their respective requirements for data access.

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