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Impact of Adherence to Ibrutinib on Clinical Outcomes in Real-World Patients With Chronic Lymphocytic Leukemia

LAUREN M. GARNER, PharmD, BCPPS, THERESA KLINE, PharmD, BCPS, BCCP, JORDAN MILLER, PharmD, BCOP, CPP, ALLISON DEAL, MS, ANQI ZHU, MS, PhD(c), MARGARET R. SKETCH, PharmD, MPH, CATHERINE C. COOMBS, MD, and BENYAM MULUNEH, PharmD, BCOP, CPP

From University of North Carolina Medical Center, Chapel Hill, North Carolina

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Lauren M. Garner, PharmD, BCPPS, 101 Manning Drive, Chapel Hill, NC 27517. E-mail: lmdrawd@g.clemson.edu

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Abstract

Background: Chronic lymphocytic leukemia (CLL) is a B-cell neoplasm with clonal expansion of small lymphocytes. Ibrutinib, an irreversible inhibitor of Bruton tyrosine kinase (BTK), is a first-line treatment option, and recent data suggest that strict adherence is directly related to clinical outcomes. **Objectives:** The primary objective of this study was to quantify ibrutinib adherence rates in real-world patients with CLL on ibrutinib; secondary outcomes included progression-free survival and overall survival. **Methods:** This retrospective study included subjects who were treated at a large academic medical center over approximately 5 years. Subjects were at least 18 years, diagnosed with CLL or small lymphocytic lymphoma, and treated with ibrutinib monotherapy for at least 6 months. Adherence was quantified using the medication possession ratio (MPR), which is the ratio of the sum of days' supply of medication in a period over the number of days in that period, and was based on fill history from the medical center's specialty pharmacy. **Results:** For the 32 subjects in this study, the mean ibrutinib adherence rate was 91.7% (range, 84.4%–100%). Only 3 subjects had disease progression, and 1 death was recorded while on therapy (all with MPR < 95%); therefore, analyses of clinical outcomes were unable to be assessed due to a low number of events. There were no statistically significant differences in rates of adherence based on baseline characteristics and adverse drug events. **Conclusion:** In patients with CLL treated with ibrutinib, mean adherence was 91.7%, which is lower than rates seen in clinical trials.

Chronic lymphocytic leukemia (CLL) is a B-cell neoplasm characterized by clonal expansion of small lymphocytes that are primarily found in the blood and bone marrow with varying involvement of lymph nodes, the liver, and the spleen. This

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B-cell malignancy is usually slow growing, with many patients remaining asymptomatic for years. Patients are typically not treated until they meet an indication for therapy such as progressive marrow failure, massive adenopathy and/or hepatosplenomegaly, or constitutional symptoms due to the CLL. Small lymphocytic lymphoma (SLL) is another manifestation of this disease, with abnormal lymphocytes accumulating in the lymph nodes with $< 5 \times 10^9$/L circulating clonal B lymphocytes. Chronic lymphocytic leukemia and SLL are often treated with a similar approach (Deeks et al., 2017). In the United States, approximately 21,000 patients are diagnosed with CLL annually, with the vast majority of diagnoses occurring in patients at least 60 years old (Siegel, Miller, & Jemal, 2018).

Ibrutinib (Imbruvica) is an orally bioavailable, irreversible inhibitor of Bruton tyrosine kinase (BTK), a B-cell signaling protein, which was first approved for use in patients with CLL in 2014. BTK plays an important role in B-cell proliferation, survival, and migration. Significantly higher levels of BTK phosphorylation are seen in malignant B cells of CLL patients (Kaur & Swami, 2017). The inhibition of BTK by ibrutinib interrupts autophosphorylation causing a reduction in downstream targets of B-cell receptor activation, which leads to reductions in B-cell proliferation (Woyach et al., 2014). Guidelines developed by the National Comprehensive Cancer Network (NCCN) include ibrutinib as an option for first-line treatment regardless of age, performance status, and cytogenetics (NCCN, 2019).

These recommendations are derived from a number of clinical trials demonstrating the clinical benefit of ibrutinib in a variety of clinical settings (Byrd et al., 2013; Byrd et al., 2014; Farooqui et al., 2015; O'Brien et al., 2014). Ibrutinib monotherapy showed superiority in progression-free survival (PFS) and overall survival (OS) in CLL or SLL when compared with chlorambucil in the first-line setting and when compared with ofatumumab in the relapsed or refractory settings (Burger et al., 2015; Byrd et al., 2014). Additionally, ibrutinib has demonstrated superiority to chemoimmunotherapy regimens (Woyach et al., 2018). Alliance A041202 compared bendamustine/rituximab (Rituxan), ibrutinib/rituximab, and ibrutinib monotherapy and demonstrated a superior PFS in the ibrutinib-containing arms; no OS benefit was seen likely due to the crossover design. Next, ECOG-ACRIN (E1912) compared fludarabine/cyclophosphamide/rituximab with ibrutinib/rituximab, demonstrating both superior PFS and OS among patients treated with ibrutinib/rituximab (Shanafelt et al., 2019).

Ibrutinib is generally well tolerated with common side effects including gastrointestinal adverse effects, upper respiratory infections, myelosuppression, bruising, and musculoskeletal pain. Although less common, hypertension, bleeding, and atrial fibrillation can occur as well (Pharmacyclics LLC, 2013). In the previously discussed study comparing ibrutinib to chlorambucil, the discontinuation rate due to adverse effects was only 9% (Burger et al., 2015). Many of ibrutinib's side effects can be mitigated through avoidance of drug-drug interactions and symptom management.

In a retrospective review of the RESONATE trial examining ibrutinib vs. ofatumumab, mean overall adherence to ibrutinib was 95%. However, this was in a highly monitored clinical trial in which subjects had close follow-up with study investigators (Barr et al., 2017). The objective of this study was to determine the rate of ibrutinib adherence in a real-world population (RWP) with CLL and if patients with adherence ≥ 95% achieved longer median PFS and OS compared to those who achieved < 95% adherence.

METHODS

Study Design

This retrospective chart review evaluated North Carolina Cancer Hospital patients who were prescribed ibrutinib between January 1, 2013, and July 1, 2018. To be included in this study, patients must have been 18 years of age, have a documented diagnosis of CLL or SLL, and been treated with ibrutinib monotherapy for at least 6 months. Subjects must have filled ibrutinib at the University of North Carolina (UNC) Shared Services Center Pharmacy. All data were collected from the health system's electronic medical record. This study was approved by the site's institutional review board. Due to the retrospective nature of the study and minimal risk to subjects, it was granted waivers for informed consent and HIPPA authorization.

Outcomes

The primary outcome of this study was the rate of medication adherence in RWP on ibrutinib monotherapy. Secondary outcomes included PFS and OS in patients, reasons for discontinuation, and safety concerns via adverse drug events. Adherence was quantified through the use of the MPR, which is the ratio of the sum of days' supply of medication in a period over the number of days in that period for a minimum of 3 months (Steiner, Koepsell, Fihn, & Inui, 1988). Adherence data were provided by the UNC Shared Services Center Specialty Pharmacy. Progression-free survival was defined using the International Workshop on Chronic Lymphocytic Leukemia criteria (time from ibrutinib initiation to documented objective disease progression or death). Overall survival was measured from ibrutinib initiation until death from any cause (Hallek et al., 2008). Adverse events were characterized by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (National Cancer Institute, 2017).

Statistical Methods

Data collected by the study investigators were managed using the Research Electronic Data Capture (REDCap) software application (Harris et al., 2009). Descriptive statistics were used to characterize the patient population. Categorical variables were used to summarize counts and percentages which were then analyzed through Fisher's exact test. Continuous variables were presented as means and analyzed through non-parametric Wilcoxon Rank Sum tests. Statistical significance was set at a two-sided significance level of .05 ($p \leq .05$).

RESULTS

A total of 32 subjects were identified who met inclusion criteria during the specified time period of this study. Figure 1 outlines how subjects were enrolled with the exclusion criteria applied to the potentially eligible subjects in the order of indication other than CLL or SLL, filling ibrutinib at an outside pharmacy, and duration < 6 months. Tables 1 and 2 outline baseline characteristics and oncologic history, respectively, based on data acquired prior to patient initiation of ibrutinib. The mean age of this population at diagnosis was 60.2 years. Most patients in this study were diagnosed with CLL (84.4%), and 53.1% of patients were male. Ibrutinib was utilized in a variety of settings: first line (34.4%), second line (31.3%), and third line or greater in therapy (31.3%). Hypertension, a known side effect of ibrutinib, was a common comorbidity noted in 37.5% of subjects prior to the start of ibrutinib. The majority of these patients (67.7%) had Medicare insurance. The recommended starting dose of ibrutinib at 420 mg daily was used in 97% of these patients. However, at the end of the study period, only 78% remained on that dose.

The distribution of MPR is depicted in Figure 2. The mean adherence rate as measured by MPR was 91.7% (range, 84.4%–100%). Twenty-six patients (81%) had adherence < 95%; in 6 of these patients, adherence was < 90%. Of the 32 subjects included in this study, only 3 had disease progres-

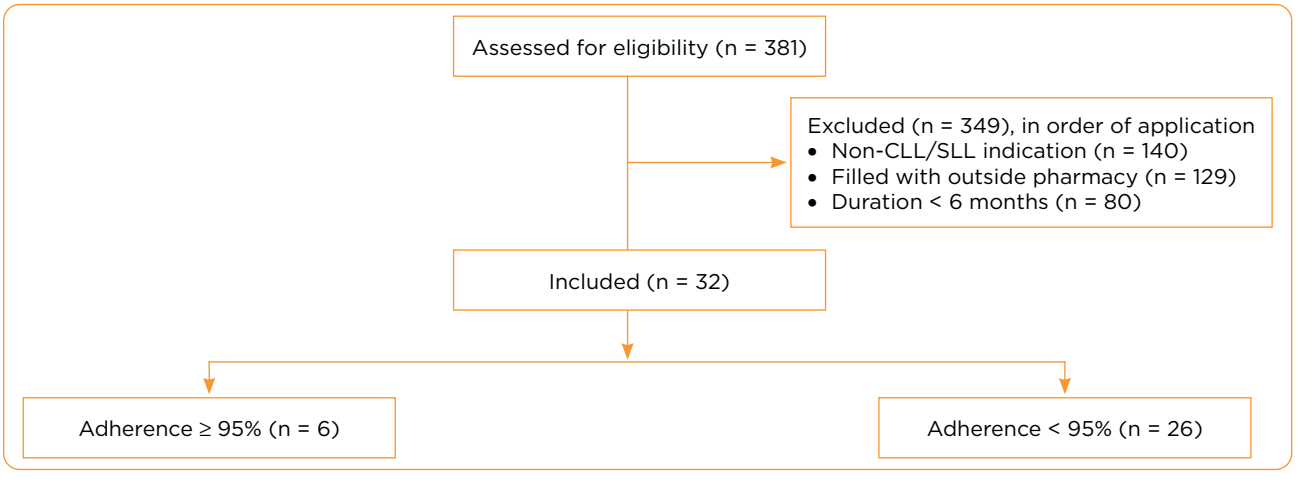

Figure 1. CONSORT diagram.

Table 1. Subject Baseline Characteristics

	Total (n = 32)	MPR ≥ 95% (n = 6)	MPR < 95% (n = 26)	*p* value
Age (years)				
Age at diagnosis, mean (years)	60.2	60.15	60.16	.9801
Age at ibrutinib initiation, mean (years)	65.97	62.64	66.77	.6348
Gender, male	53.1% (n = 17)	66.7% (n = 4)	50% (n = 13)	.6586
Insurance				
Medicaid	6.3% (n = 2)	–	7.7% (n = 2)	–
Medicare	67.7% (n = 21)	66.7% (n = 4)	65.4% (n = 17)	–
Private insurance	29% (n = 9)	33.3% (n = 2)	27% (n = 7)	–
Financial assistance				
Grant	21.8% (n = 7)	16.7% (n = 1)	23% (n = 6)	–
Copay card	12.5% (n = 4)	33.3% (n = 2)	7.7% (n = 2)	–
Past medical history				
Atrial fibrillation or flutter	3.1% (n = 1)	–	3.8% (n = 1)	1
Hypertension	37.5% (n = 12)	50% (n = 3)	34.6% (n = 9)	.6471
Prior intracranial hemorrhage	–	–	–	–
Prior GI bleed	6.3% (n = 2)	–	7.7% (n = 2)	1
Chronic kidney disease	12.5% (n = 4)	–	15.3% (n = 4)	.5662
Baseline laboratory values, mean				
Hemoglobin (g/dL)	12.02 (n = 32)	13.63 (n = 6)	11.65 (n = 26)	.0564
Hematocrit (%)	36.03 (n = 32)	40.28 (n = 6)	35.05 (n = 26)	.0865
Platelets ($\times 10^9$/L)	157.94 (n = 32)	183.5 (n = 6)	152.04 (n = 26)	.5144
Absolute lymphocyte count ($\times 10^9$/L)	37.57 (n = 32)	31.23 (n = 6)	39.15 (n = 26)	.7754
Serum creatinine (mg/dL)	1.09 (n = 28)	0.95 (n = 6)	1.13 (n = 22)	.4666
AST (U/L)	26.46 (n = 26)	27.6 (n = 5)	26.19 (n = 21)	.4930
ALT (U/L)	29.62 (n = 26)	30 (n = 5)	29.52 (n = 21)	.8450
Uric acid (mg/dL)	5.79 (n = 11)	5.3 (n = 2)	5.9 (n = 9)	.8132
LDH (IU/L)	538.48 (n = 25)	859 (n = 5)	458.35 (n = 20)	.0191
Beta-2 microglobulin (mg/L)	4.74 (n = 8)	3.26 (n = 3)	5.63 (n = 5)	.5510

Note. Baseline considered as time of ibrutinib initiation unless otherwise noted. GI = gastrointestinal; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase.

sion, and 2 deaths were recorded, only 1 of which was on therapy at the time of death. Patients with disease progression and death had an MPR < 95%.

Figures 3 and 4 depict the time-to-event analyses for PFS and OS, respectively. However, because of the low event rates, it is likely inappropriate to state that adherence does not have an impact on PFS and OS based on this small dataset alone. Ibrutinib was permanently discontinued in 14 patients (43.8%), most commonly due to an adverse drug event (ADE) with a higher rate in the higher adherence group compared with the lower adherence group (33.3% vs. 15.4%, respectively). The most commonly reported ADE in this study was minor bleeding, and there were no reports of new or worsening atrial fibrillation. There were no statistically significant differences in rates of adherence based on baseline demographic and lab test characteristics or adverse drug events. Although there was a difference in rates of cytogenetic mark-

Table 2. Oncologic History

	Total (n = 32)	MPR ≥ 95% (n = 6)	MPR < 95% (n = 26)
Chronic lymphocytic leukemia	84.4% (n = 27/32)	83.3% (n = 5)	84.6% (n = 22)
Small lymphocytic lymphoma	15.6% (n = 5/32)	16.7% (n = 1)	15.4% (n = 4)
Cytogenetics (n = 26)			
13q deletion	31% (n = 8/26)	66.7% (n = 4/6)	20% (n = 4/20)
Normal FISH/karyotype	15.4% (n = 4/26)	0% (n = 0/6)	20% (n = 4/20)
Trisomy 12	23% (n = 6/26)	16.7% (n = 1/6)	25% (n = 5/20)
11q deletion	19.2% (n = 5/26)	33.3% (n = 2/6)	15% (n = 3/20)
17p deletion	19.2% (n = 5/26)	50% (n = 3/6)	10% (n = 2/20)
TP53 mutation	50% (n = 1/2)	100% (n = 1/1)	0% (n = 0/1)
Complex karyotype	31% (n = 8/26)	50% (n = 3/6)	25% (n = 5/20)
IGHV unmutated	100% (n = 4/4)	100% (n = 2/2)	100% (n = 2/2)
Rai stage (n = 32)			
Low (stage 0)	6.3% (n = 2/32)	16.7% (n = 1/6)	3.8% (n = 1/26)
Intermediate (stage I–II)	31.3% (n = 10/32)	33.3% (n = 2/6)	30.1% (n = 8/26)
High (stage III–IV)	62.5% (n = 20/32)	50% (n = 3/6)	65.4% (n = 17/26)
Line in therapy (n = 32)			
First	34.4% (n = 11/32)	66.7% (n = 4/6)	27% (n = 7/26)
Second	31.3% (n = 10/32)	16.7% (n = 1/6)	34.6% (n = 9/26)
Third or greater	31.3% (n = 10/32)	16.7% (n = 1/6)	34.6% (n = 9/26)

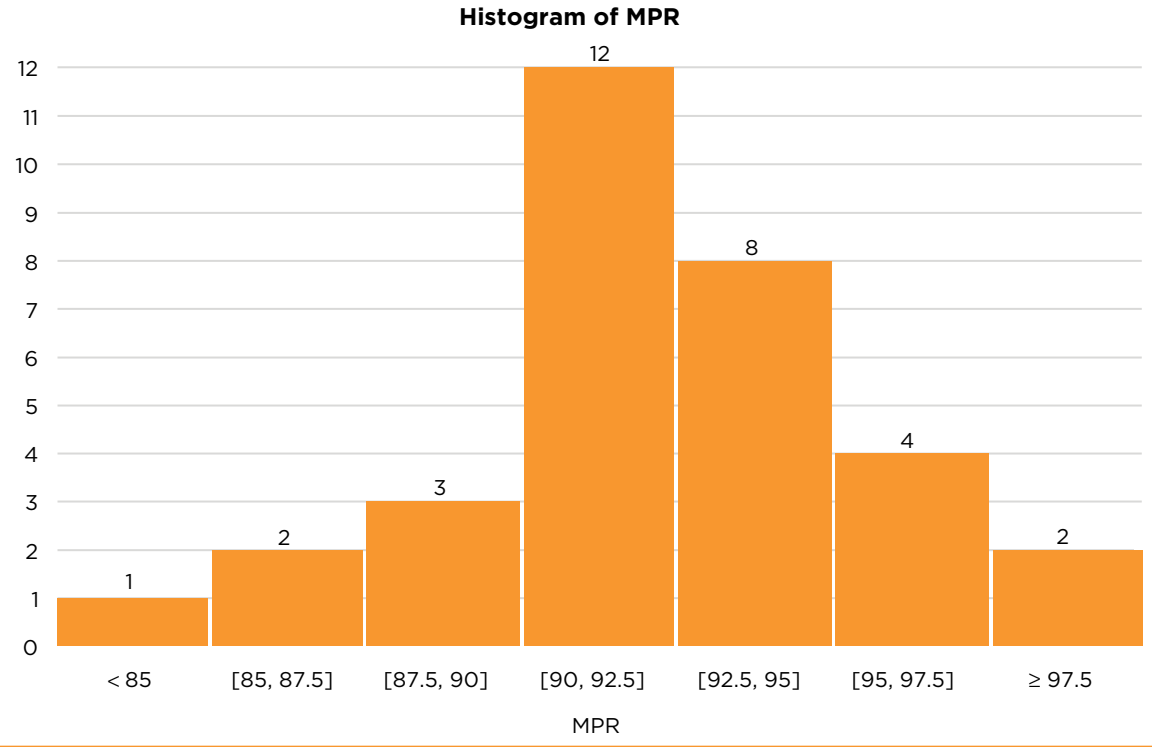

Figure 2. Distribution of medication possession ratios (MPR).

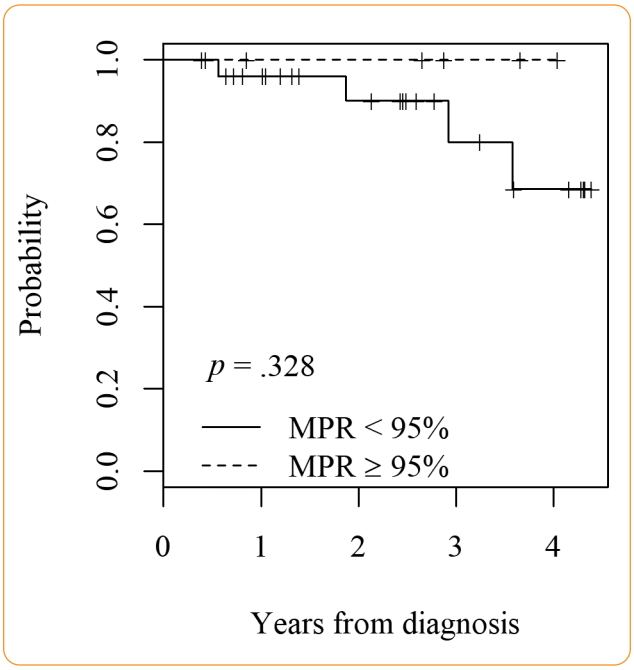

Figure 3. Kaplan-Meier of progression-free survival by MPR group.

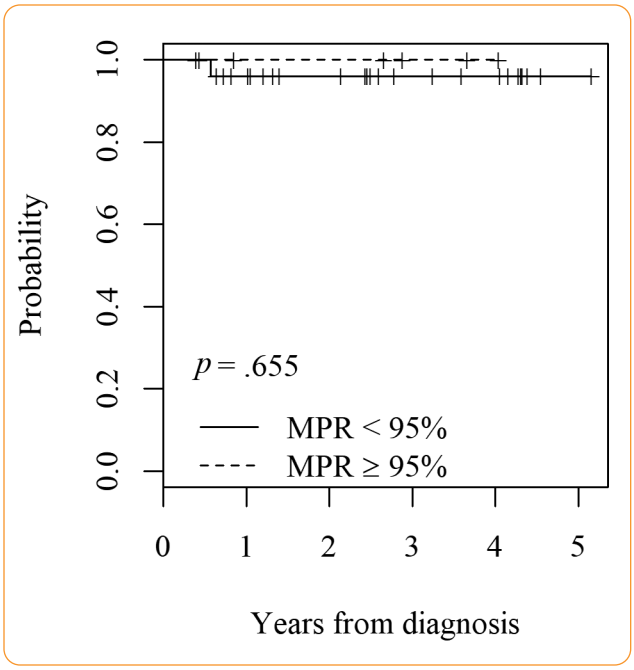

Figure 4. Kaplan-Meier of overall survival by MPR group.

ers between the two groups, this is thought to be a spurious finding and not truly linked to ibrutinib adherence. Patients who had shorter time between diagnosis to ibrutinib initiation had higher adherence (85 vs. 30 months, $p = .0296$). Ibrutinib history is outlined for both groups in Table 3.

DISCUSSION

In other chronic disease states, there are clear relationships between medication adherence and clinical outcomes. For example, when compared with patients who had adherence ≤ 90%, patients with > 90% adherence to imatinib for chronic myeloid leukemia had dramatically higher rates of major molecular response (94.5% vs. 28.4%, $p < .001$) and complete molecular response at 6 years (43.8% vs. 0%, $p = .002$; Marin et al., 2010). Recent data have suggested that strict adherence to ibrutinib, assessed by dose intensity over the first 8 weeks of therapy, is directly related to clinical outcomes for patients with CLL. Subjects with higher-than-average dose intensities over the first 8 weeks of therapy (mean 96%) had longer PFS and higher OS rates than subjects with lower-than-average dose intensities (Barr et al., 2017). However, a major limitation to applying this information in clinical practice stems from the study's generalizability. All subjects were enrolled in a phase III clinical trial with close monitoring and follow-up by study investigators. Additionally, long-term medication adherence was not assessed. The rate of adherence to ibrutinib and how it may impact clinical outcomes in RWP has not yet been assessed.

To date, this is the first study quantifying adherence in a RWP of CLL patients on ibrutinib monotherapy. Adverse events seen in ibrutinib clinical trials include diarrhea, bleeding, and increased rates of atrial fibrillation (Pharmacyclics LLC, 2013). Within this study, there were no reports of atrial fibrillation onset or worsening; however, there were 10 patients who experienced a minor bleed according to the CTCAE version 5.0 criteria.

This study demonstrated high discontinuation rates (43.8%), which includes the 18.8% of subjects who discontinued due to adverse effects. In comparison, the discontinuation rate due to adverse effects was 4% in the RESONATE study and 9% in the RESONATE-2 study, suggesting that patients outside of a clinical trial setting are not able to tolerate ibrutinib as well due to ADEs (Burger et al., 2015; Byrd et al., 2013).

Limitations of this study include the small sample size, partially due to challenges of obtaining fill history from outside pharmacies. Also,

Table 3. Ibrutinib History

	Total (n = 32)	MPR ≥ 95% (n = 6)	MPR < 95% (n = 26)	*p* value
Ibrutinib starting dose				
280 mg	3.1% (n = 1)	–	3.8% (n = 1)	1
420 mg	96.9% (n = 31)	100% (n = 6)	86.2% (n = 25)	
Medication possession ratio				
Mean	91.7%	97%	90.6%	0.0002
Median	92%	96%	91%	–
Final ibrutinib dose				
280 mg	21.8% (n = 7)	–	26.9% (n = 7)	0.2964
420 mg	78.1% (n = 25)	100% (n = 6)	73.1% (n = 19)	
Reasons for discontinuation				
Total discontinuation	43.8% (n = 14)	50% (n = 3)	42.3% (n = 11)	1
Adverse reactions	18.8% (n = 6)	33.3% (n = 2)	15.4% (n = 4)	0.3104
Disease progression	9.4% (n = 3)	–	11.5% (n = 3)	1
Death	6.3% (n = 2)	16.7% (n = 1)	3.8% (n = 1)	0.3448
Change in goals of care	6.3% (n = 2)	–	7.7% (n = 2)	1
Other	3.1% (n = 1)	–	3.8% (n = 1)	1
Length of therapy before discontinuation				
Mean (days)	573	534	584	0.755
Median (days)	492	362	613	–

Note. MPR = medication possession ratio.

patients were only included if they were treated with ibrutinib monotherapy for 6 months. Unfortunately, 80 patients were excluded based on this criterion alone; therefore, it is reasonable to increase follow-up and monitoring during the first 6 months of treatment to avoid discontinuation of therapy. Progression of CLL within the first 6 months of diagnosis is rare because of the slow-growing nature of the disease, and with the known efficacy of ibrutinib in the treatment of CLL, it is speculated that the majority of patients were excluded due to potential adverse effects. The requirement for 6 months of therapy prior to inclusion in this study may have unintentionally selected for patients at lower risk of adverse drug events with ibrutinib because they had been able to tolerate the drug for at least 6 months without therapy discontinuation. Because of the small sample size, authors included patients with less than 6 months of fill history on file with the institution's pharmacy and calculated MPR using the data available, as long as it was documented within the chart that these patients were still actively taking ibrutinib, but filling with another pharmacy.

Another limitation of this study is the inability to quantify the number of days ibrutinib was held due to a provider's request or due to lack of tolerability. When undergoing a procedure, patients were frequently instructed to hold ibrutinib due to the risk of bleeding. However, the length of time the medication was held was not specified in all patient charts. Although both holding ibrutinib for a procedure and patient-initiated nonadherence may result in a lower MPR, procedural holds are unavoidable, thus increasing the importance of improving patient-driven adherence.

Close monitoring within the first 6 months of therapy initiation and increased mitigation of adverse effects has the potential to decrease discontinuation rates in RWP of CLL patients on ibrutinib monotherapy. In clinical practice, there are often programs and mechanisms in place to encourage adherence to medications deemed high

risk for poor outcomes with poor adherence such as imatinib for chronic myelogenous leukemia and antiretrovirals for HIV. Advanced practitioners, including pharmacists with advanced training or certifications, nurse practitioners, and physician assistants, are well equipped to fill this unmet need in CLL treatment. Clinical pharmacists are uniquely positioned to help overcome barriers of nonadherence by establishing oral chemotherapy management programs that address factors such as toxicity mitigation (avoidance of drug-drug interactions, self-management strategies) and overseeing financial toxicity concerns (partnering with medication assistance specialists, anticipating insurance barriers, etc). Our study provides justification for the establishment of such programs for ibrutinib in CLL. Although data presented are limited due to numbers, the lower-than-expected adherence seen in our series provides justification for the establishment of such programs for ibrutinib in CLL.

CONCLUSION

In 32 patients with CLL treated with ibrutinib monotherapy, mean adherence was 91.7%, which is lower than rates observed in clinical trials. Only 6 patients had adherence ≥ 95%. Although effects of adherence on PFS and OS were unable to be analyzed in this study, discontinuation rates were four times as high as those seen in clinical trials (43.8% vs. 9%), underscoring the need for tolerability management to reduce therapy discontinuation and improve adherence in patients taking ibrutinib monotherapy.

Disclosure

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