

Atrial Fibrillation and Bleeding in Patients With Chronic Lymphocytic Leukemia Treated with Ibrutinib in the Veterans Health Administration

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Background: Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in adults. The introduction of novel oral agents, starting with ibrutinib in 2013, has revolutionized the therapeutic landscape; however, clinical trials have suggested an association between ibrutinib and the risk of bleeding-related adverse events and atrial fibrillation (Afib) in patients with CLL.

Methods: Patients diagnosed and treated for CLL at the Veterans Health Administration (VHA) from 2010 to 2014 were followed until December 31, 2016, death, or lack of utilization of hematology/oncology services for ≥ 18 months; or until incidence of another cancer. Treatments dispensed, evidence of VHA system use, bleeding events, and Afib were determined from the administrative records, laboratory records, pharmacy dispensation records, and clinical notes in the electronic healthcare record.

Results: From 2010 to 2014, 2,796 patients were diagnosed

and received care for CLL within the VHA, of whom 172 patients received ibrutinib and 291 received bendamustine + rituximab (BR). The use of anticoagulants following induction therapy did not differ between BR and ibrutinib patients (9% vs 8%, respectively), nor did the use of antiplatelets agents (6% vs 2%, respectively). Of the 291 patients that received BR, 12 (4%) developed a bleeding event compared with 20 (12%) who received ibrutinib. Additionally, 13 (8%) ibrutinib patients developed Afib compared with 9 (3%) BR patients.

Conclusions: Real-world evidence from a nationwide cohort of patients with CLL suggests that while ibrutinib is associated with increased bleeding-related adverse events and Afib, the risk is comparable to those reported in previous clinical trials. These findings suggest that patients in real-world clinical care settings with higher levels of comorbidities may be at an increased risk for bleeding events and Afib.

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Chronic lymphocytic leukemia (CLL) is the most common leukemia diagnosed in developed countries, with an estimated 21,040 new diagnoses of CLL expected in the US in 2020.¹⁻³ CLL is an indolent cancer characterized by the accumulation of B-lymphocytes in the blood, marrow, and lymphoid tissues.⁴ It has a heterogeneous clinical course; the majority of patients are observed or receive delayed treatment following diagnosis, while a minority of patients require immediate treatment. After first-line treatment, some patients experience prolonged remissions while others require retreatment within 1 or 2 years. Fortunately, advances in cancer biology and therapeutics in the last decade have increased the number of treatment options available for patients with CLL.

Until recently, most CLL treatments relied on a chemotherapy or a chemoimmunotherapy backbone; however, the last few years have seen novel therapies introduced, such as small molecule inhibitors to target molecular pathways that promote the normal development, expansion, and survival of B-cells.⁵ One such therapy is ibrutinib, a targeted Bruton tyrosine kinase inhibitor that received accelerated approval by the US Food and Drug Administration (FDA) in February 2014 for patients with CLL who received

at least 1 prior therapy. The FDA later expanded this approval to include use of ibrutinib in patients with CLL with relapsed or refractory disease, with or without chromosome 17p deletion. In 2016, based on data from the RESONATE-17 study, the FDA approved ibrutinib for first-line therapy in patients with CLL.⁶

Ibrutinib's efficacy, ease of administration and dosing (all doses are oral and fixed, rather than based on weight or body surface area), and relatively favorable safety profile have resulted in a rapid growth in its adoption.⁷ Since its adverse event (AE) profile is generally more tolerable than that of a typical chemoimmunotherapy, its use in older patients with CLL and patients with significant comorbidities is particularly appealing.⁸

However, the results of some clinical trials suggest an association between treatment with ibrutinib and an increased risk of bleeding-related events of any grade (44%) and major bleeding events (4%).^{7,8} The incidence of major bleeding events was reported to be higher (9%) in one clinical trial and at 5-year follow-up, although this trial did not exclude patients receiving concomitant oral anticoagulation with warfarin.^{6,9}

Heterogeneity in clinical trials' definitions of major bleeding confounded the ability to

calculate bleeding risk in patients treated with ibrutinib in a systematic review and meta-analysis that called for more data.¹⁰ Additionally, patients with factors that might increase the risk of major bleeding with ibrutinib treatment were likely underrepresented in clinical trials, given the carefully selected nature of clinical trial subjects. These factors include renal or hepatic disease, gastrointestinal disease, and use of a number of concomitant medications such as antiplatelets or anticoagulant medications. Accounting for use of the latter is particularly important because patients who develop atrial fibrillation (Afib), one of the recognized AEs of treatment with ibrutinib, often are treated with anticoagulant medications in order to decrease the risk of stroke or other thromboembolic complications.

A single-site observational study of patients treated with ibrutinib reported a high utilization rate of antiplatelet medications (70%), anticoagulant medications (17%), or both (13%) with a concomitant major bleeding rate of 18% of patients.¹¹ Prevalence of bleeding events seemed to be highly affected by the presence of concomitant medications: 78% of patients treated with ibrutinib while concurrently receiving both antiplatelet and anticoagulant medications developed a major bleeding event, while none of the patients who were not receiving antiplatelets, anticoagulants, or medications that interact with cytochrome P450 (an enzyme that metabolized chemotherapeutic agents used to treat cancer) experienced a major bleeding event.¹¹

The prevalence of major bleeding events, comorbidities, and utilization of medications that could increase the risk of major bleeding in patients with CLL on ibrutinib in the Veterans Health Administration (VHA) is not known. The VHA is the largest integrated health care system in the US. To address these knowledge gaps, a retrospective observational study was conducted using data on demographics, comorbidities that could affect bleeding, use of anticoagulant and antiplatelet medications, and bleeding events in patients with CLL who were treated in the first year of ibrutinib availability from the VHA.

The first year of ibrutinib availability was chosen for this study since we anticipated that many health care providers would be unfamiliar with ibrutinib during that time given its novelty, and therefore more likely to codispense ibrutinib with medications that could increase the risk

of a bleeding event. Since Afib is both an AE associated with ibrutinib treatment and a condition that often is treated with anticoagulants, the prevalence of Afib in this population was also included. For context, the incidence of bleeding and Afib and use of anticoagulant and antiplatelet medications during treatment in a cohort of patients with CLL treated with bendamustine + rituximab (BR) also was reported.

METHODS

The VHA maintains the centralized US Department of Veterans Affairs Cancer Registry System (VACRS), with electronic medical record data and other sources captured in its Corporate Data Warehouse (CDW). The VHA CDW is a national repository comprising data from several VHA clinical and administrative systems. The CDW includes patient identifiers; demographics; vital status; lab information; administrative information (such as diagnostic *International Statistical Classification of Diseases and Related Health Problems* [ICD-9] codes); medication dispensation tables (such as outpatient fill); IV package information; and notes from radiology, pathology, outpatient and inpatient admission, discharge, and daily progress.

Registrars abstract all cancer cases within the VHA system (or diagnosed outside the VHA, if patients subsequently receive treatment in the VHA). It is estimated that VACRS captures 3% of cancer cases in the US.¹² Like most registries, VACRS captures data such as diagnosis, age, gender, race, and vital status.

The study received approval from the University of Utah Institutional Review Board and used individual patient-level historical administrative, cancer registry, and electronic health care record data. Patients diagnosed and treated for CLL at the VHA from 2010 to 2014 were identified through the VACRS and CDW; patients with a prior malignancy were excluded. Patients who received ibrutinib or BR based on pharmacy dispensation information were selected. Patients were followed until December 31, 2016 or death; patients with documentation of another cancer or lack of utilization of the VHA hematology or oncology services (defined as absence of any hematology and/or oncology clinic visits for ≥ 18 months) were omitted from the final analysis (Figure).

Previous and concomitant utilization of antiplatelet (aspirin, clopidogrel) or anticoagulant (dalteparin, enoxaparin, fondaparinux, heparin,

rivaroxaban, and warfarin) medications was extracted 6 months before and after the first dispensation of ibrutinib or BR using pharmacy dispensation records.

Study Definitions

Prevalence of comorbidities that could increase bleeding risk was determined using administrative ICD-9-CM codes. Liver disease was identified by presence of cirrhosis, hepatitis C virus, or alcoholic liver disease using administrative codes validated by Kramer and colleagues, who reported positive and negative predictive values of 90% and 87% for cirrhosis, 93% and 92% for hepatitis C virus, and 71% and 98% for alcoholic liver disease.¹³ Similarly, end-stage liver disease was identified using a validated coding algorithm developed by Goldberg and colleagues, with a positive predictive value of 89.3%.¹⁴ The presence of controlled or uncontrolled diabetes mellitus (DM) was identified using the procedure described by Guzman and colleagues.¹⁵ Quan's algorithm was used to calculate Charlson Comorbidity Index (CCI) based on ICD-9-CM codes for inpatient and outpatient visits within a 6-month lookback period prior to treatment initiation.¹⁶

A major bleeding event was defined as a hospitalization with an ICD-9-CM code suggestive of major bleeding as the primary reason, as defined by Lane and colleagues in their study of major bleeding related to warfarin in a cohort of patients treated within the VHA.¹⁷ Incidence rates of major bleeding events were identified during the first 6 months of treatment. Incidence of Afib—defined as an inpatient or outpatient encounter with the 427.31 ICD-9-CM code—also was examined within the first 6 months after starting treatment. The period of 6 months was chosen because bendamustine must be discontinued after 6 months.

Study Analysis

Descriptive statistics were used to examine patient demographics, disease characteristics, and treatment history from initial CLL diagnosis through end of study observation period. Categorical variables were summarized using frequencies and accompanying proportions, while a mean and standard deviation were used to summarize continuous variables. For the means of continuous variables and of categorical data, 95% CIs were used. Proportions and

accompanying 95% CIs characterized treatment patterns, including line of therapy, comorbidities, and bleeding events. Treatment duration was described using mean and accompanying 95% CI. Statistical tests were not conducted for comparisons among treatment groups. Patients were censored at the end of follow-up, defined as the earliest of the following scenarios: (1) end of study observation period (December 31, 2016); (2) development of a secondary cancer; or (3) last day of contact given absence of care within the VHA for ≥ 18 months (with care defined as oncology and/or oncology/hematology visit with an associated note). Analysis was performed using R 3.4.0.

RESULTS

Between 2010 and 2014, 2,796 patients were diagnosed and received care for CLL within the VHA. Overall, all 172 patients who were treated with ibrutinib during our inclusion period were selected. These patients were treated between January 1, 2014 and December 31, 2016, following ibrutinib's approval in early 2014. An additional 291 patients were selected who received BR (Table). Reflecting the predominantly male population of the VHA, 282 (97%) BR patients and 167 (97%) ibrutinib patients were male. The median age at diagnosis was 67 years for BR patients and 69 years for ibrutinib patients. About 76% of patients who received ibrutinib and 82% of patients who received BR were non-Hispanic white; 17% and 14% were African American, respectively.

Less than 10% of patients receiving either ibrutinib or BR had liver disease per criteria used by Kramer and colleagues, or end-stage liver disease using criteria developed by Goldberg and colleagues.^{12,13} About 5% of patients had a history of previous bleeding in the 6-month period prior to initiating either therapy. Mean CCI (excluding malignancy) score was 1.5 (range, 0-11) for the ibrutinib group, and 2.1 (range, 0-9) for the BR group. About 16% of the ibrutinib group had controlled DM and fewer than 10% had uncontrolled DM, while 4% of patients in the BR group met the criteria for controlled DM and another 4% met the criteria for uncontrolled DM.

There was very low utilization of anticoagulant or antiplatelet medication prior to initiation of ibrutinib (2.9% and 2.3%, respectively) or BR (< 1% each). In the first 6 months after treatment

TABLE First-Line Treatment in Patients with Chronic Lymphocytic Leukemia

Patient Characteristics	Bendamustine + Rituximab			Ibrutinib		
	All (N = 291)	No bleeding (n = 283)	Bleeding (n = 8)	All (N = 172)	No bleeding (n = 158)	Bleeding (n = 14)
Median age, y	67	67	69	69	69	70
Age ≥ 70, No. (%)	116 (40)	112 (40)	^a	80 (47)	73 (46)	7 (50)
Male, No. (%)	282 (97)	275 (97)	7 (88)	167 (97)	154 (98)	13 (93)
Race, No. (%)						
Non-Hispanic white	240 (82)	235 (84)	5 (71)	130 (76)	119 (79)	11 (85)
Black	42 (14)	40 (14)	^a	30 (17)	28 (19)	^a
Other/missing	^a	^a	^a	^a	^a	^a
Comorbidities at treatment initiation						
Liver disease, No. (%) ¹³	8 (3)	8 (3)	^a	6 (3)	6 (4)	^a
End-stage liver disease, No. (%) ¹⁴	26 (9)	25 (88)	^a	11 (6)	11 (7)	^a
Diabetes mellitus, No. (%)						
Uncontrolled	13 (4)	13 (4)	^a	15 (9)	14 (10)	^a
Controlled	11 (4)	11 (4)	^a	27 (16)	26 (17)	^a
Previous bleeding event(s), No. (%)	16 (6)	14 (5)	^a	7 (4)	^a	^a
Charlson Comorbidity Index, mean (range)	2 (0-9)	2 (0-9)	3 (0-5)	2 (0-11)	1 (0-11)	2 (0-8)
Previous usage prior to induction therapy						
Anticoagulants, No. (%)	^a	^a	^a	5 (3)	5 (3)	^a
Antiplatelets, No. (%)	^a	^a	^a	^a	^a	^a
Concomitant usage following induction therapy						
Anticoagulants, No. (%)	24 (8)	24 (9)	^a	13 (8)	10 (6)	^a
Antiplatelets, No. (%)	14 (5)	14 (5)	^a	^a	^a	^a
Bleeding events and atrial fibrillation ^b						
Bleeding events, No. (%)	8 (3)	-	-	14 (8)	-	-
Median time to onset, d	49			64		
Atrial Fibrillation, No. (%)	9 (4)			13 (8)		
Median time to onset, d	19			96		

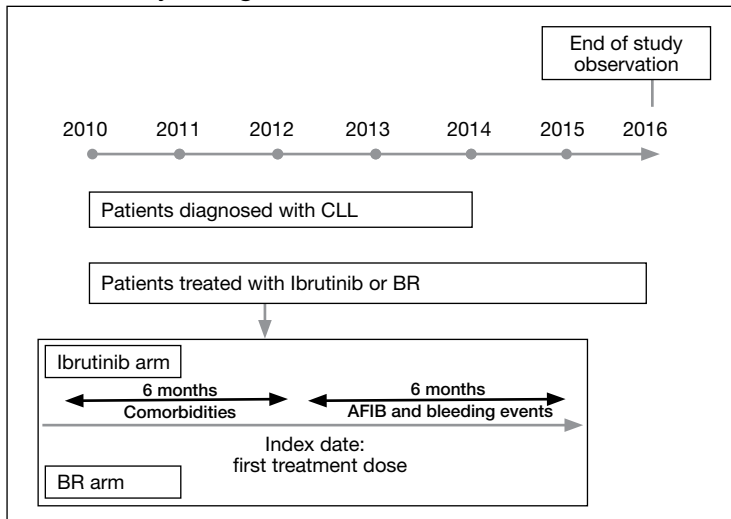
^aFewer than 5 patients identified.

^bWithin 6 months following the start of therapy.

initiation, about 8% of patients in both ibrutinib and BR cohorts received anticoagulant medication while antiplatelet utilization was < 5% in either group.

In the BR group, 8 patients (2.7%) experienced a major bleeding event, while 14 patients (8.1%) in the ibrutinib group experienced a bleeding event ($P = .008$). While these numbers were too low to perform a formal statistical analysis of the association between clinical covariates and bleeding in either group, there did not seem to be an association between bleeding and liver disease or DM. Of patients

who experienced a bleeding event, about 1 in 4 patients had had a prior bleeding event in both the ibrutinib and the BR groups. Interestingly, while none of the patients who experienced a bleeding event while receiving BR were taking concomitant anticoagulant medication, 3 of the 14 patients who experienced a bleeding event in the ibrutinib group showed evidence of anticoagulant utilization. Finally, the incidence of Afib (defined as patients with no evidence of Afib in the 6 months prior to treatment but *with* evidence of Afib in the 6 months following treatment initiation) was 4% in the BR

FIGURE Study Design Schema

Abbreviations: Afib; atrial fibrillation; BR, bendamustine + rituximab; CLL, chronic lymphocytic leukemia.

group, and about 8% in the ibrutinib group ($P = .003$).

DISCUSSION

To the authors' knowledge, this study is the first to examine the real-world incidence of bleeding and Afib in veterans who received ibrutinib for CLL in the first year of its availability. The study found minimal use of anticoagulants and/or antiplatelet agents prior to receiving first-line ibrutinib or BR, and very low use of these agents in the first 6 months following the initiation of first-line treatment. This finding suggests a high awareness among VA providers of potential adverse effects (AEs) of ibrutinib and chemotherapy, and a careful selection of patients that lack risk factors for AEs.

In patients treated with first-line ibrutinib when compared with patients treated with first-line BR, moderate increases in bleeding (2.7% vs 8.1%, $P = .008$) and Afib (10.5% vs 3%, $P = .003$) also were observed. These results are concordant with previous findings examining the use of ibrutinib in patients with CLL.¹⁸⁻²⁰

Limitations

The results of this study should be interpreted with caution, as some limitations must be considered. The study was conducted in the early days of ibrutinib adoption. Since then, more patients have been treated with ibrutinib and for longer durations. As clinicians gain more familiarity and with ibrutinib, and as additional novel therapeutics emerge, it is possible that

the initial awareness about risks for possible AEs may diminish; patients with high comorbidity burdens and concomitant medications would be especially vulnerable in cases of reduced physician vigilance.

Another limitation of this study stems from the potential for dual system use among patients treated in the VHA. Concurrent or alternating use of multiple health care systems (use of VHA and private-sector facilities) may present gaps in the reconstruction of patient histories, resulting in missing data as patients transition between commercial, the Centers for Medicare and Medicaid Services, and VHA care. As a result, the results presented here do not reflect instances where a patient experienced a bleeding event treated outside the VA.

Problems with missing data also may occur due to incomplete extraction from the electronic health record; these issues were addressed by leveraging an understanding of the multiple data marts within the CDW environment to harmonize missing and/or erroneous information through use of other data marts when possible. Lastly, this research represents a population-level study of the VHA, thus all findings are directly relevant to the VHA. The generalizability of the findings outside the VHA would depend on the characteristics of the external population.

CONCLUSION

Real-world evidence from a nationwide cohort of veteran patients with CLL treated with ibrutinib suggest that, while there is an association of increased bleeding-related events and Afib, the risk is comparable to those reported in previous studies.¹⁸⁻²⁰ These findings suggest that patients in real-world clinical care settings with higher levels of comorbidities may be at a slight increased risk for bleeding events and Afib.

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Author disclosures

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