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Bleeding with concomitant ibrutinib and oral anticoagulant therapy: a population-based cohort study

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To the Editor:

Ibrutinib, a Bruton's Tyrosine Kinase inhibitor, has transformed treatment strategies for B-cell malignancies including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), and marginal zone lymphoma (MZL). Clinical trials found that ibrutinib produces high progression-free survival and overall response rates in CLL, MCL, and MZL, and has a favorable safety profile compared to chemotherapy.[1] However, bleeding occurs in up to 50% of patients—sometimes leading to serious consequences such as hospitalization or death.

Given the older age and potential multimorbidity of the ibrutinib-treated population, many patients have a clinical indication for an oral anticoagulant (OAC). Moreover, up to 16% of

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Author Contributions

ND and CEL designed the study. ND, SH, and CEL secured funding for the study. ND wrote the manuscript. ND, WY, SH, JMR, AC, and CEL performed the research and provided critical review and final approval of the manuscript.

Ethics Approval Statement

The University of Pennsylvania institutional review board deemed research using this dataset exempt from review.

patients develop atrial fibrillation while taking ibrutinib,[1] further increasing the likelihood of concomitant ibrutinib and OAC treatment. While bleeding may be more frequent in patients concomitantly treated with OACs given their associated bleeding risk, data on concomitant use are limited. Clinicians are thus regularly confronted with the challenging choice to use ibrutinib in OAC-treated patients, or OACs in ibrutinib-treated patients, without sufficient knowledge of the bleeding risk. In fact, a study suggested that patients co-treated with ibrutinib and an OAC/antiplatelet have a similar major hemorrhage risk compared to patients co-treated with an alternative therapy and an OAC/antiplatelet.[2] This conclusion, however, was drawn by indirectly comparing the similarly increased major hemorrhage risk associated with OAC and/or antiplatelet use in both ibrutinib-treated patients and comparator-treated patients. To more validly assess the bleeding risk with concomitant use, a study directly comparing the bleeding rate in patients co-exposed to ibrutinib and OACs with patients co-exposed to an alternative treatment and OACs is needed. This may inform ibrutinib's benefit-harm balance in this potentially high-risk subpopulation.

We therefore conducted a retrospective cohort study to compare the real-world rate of major, clinically-relevant, and provider-diagnosed bleeding between concomitant ibrutinib + OAC treatment and concomitant bendamustine-rituximab (BR) + OAC treatment in individuals with CLL, MCL, or MZL using Optum's de-identified Clinformatics® Data Mart commercial claims. Details on Optum Clinformatics® are described in Supplemental Methods 1.1. Additionally, to elucidate the magnitude of the difference in bleeding rates between individuals concomitantly treated with ibrutinib + OACs and individuals treated with ibrutinib alone, we compared findings to our previous study[3] which assessed major and clinically-relevant bleeding rates with ibrutinib vs. BR in patients not concomitantly using OACs.

We included individuals who had incident co-exposure to an OAC and either ibrutinib or BR between November 1, 2013 and February 29, 2020, and were diagnosed with CLL, MCL, or MZL. Details on defining the study population are provided in Supplemental Methods 1.2–1.5.

Potential confounders were identified during the 6-month baseline period preceding the index date (date of incident co-exposure to an OAC + ibrutinib/BR) and are listed in Supplementary Table 1.

The primary outcome was major bleeding, defined as a bleeding event resulting in inpatient hospitalization. We used a previously validated algorithm to identify outcomes, which demonstrated a positive predictive value of 89% in health insurance claims data using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes.[4] The secondary outcome was clinically-relevant bleeding; a composite of bleeding events resulting in inpatient hospitalization (i.e., major bleeding) and those resulting in emergency department presentation. We also assessed an outcome that was specified post-hoc due to the low number of primary and secondary outcomes and the sparsity of data on bleeding of any type in this patient population. This was provider-diagnosed bleeding, which was any bleed diagnosed by a healthcare provider (see Supplemental Methods 1.6 for additional details).

We calculated descriptive statistics for baseline variables and crude incidence rates. We included pre-specified covariates into a logistic regression model to calculate the propensity score, then calculated the stabilized inverse probability of treatment weight (sIPTW). We estimated hazard ratios (HRs) using Cox proportional hazards regression, weighted using sIPTW. We also conducted a pre-specified subgroup analysis by OAC type (direct oral anticoagulant [DOAC] vs. warfarin). Additional details on primary, subgroup, and sensitivity/effect modification analyses are provided in Supplementary Methods 1.7. The University of Pennsylvania institutional review board deemed research using this dataset exempt from review.

We identified 480 and 212 concomitant users of ibrutinib + OAC and BR + OAC, respectively (Supplementary Figure 3). Individuals were predominantly male (66.3%) and White (73.0%), with a median age of 77 years and a median frailty score of 0.170 (i.e., pre-frail). Most individuals had CLL (77.9%). Differences in unweighted baseline characteristics between groups are highlighted in Supplemental Results 2.1. After weighting, all baseline characteristics included in the propensity score were well-balanced except for household income (absolute standardized difference = 0.17) (Supplementary Tables 5 and 6, Supplementary Figure 4).

DOACs were used in 72.9% and 59.0% of ibrutinib + OAC-treated and BR + OAC-treated individuals, respectively (Supplementary Table 7). Among ibrutinib + warfarin-treated individuals, 72% initiated ibrutinib while on warfarin. Additional details on concomitant OAC use are provided in Supplemental Results 2.2.

Crude incidence rates for major, clinically-relevant, and provider-diagnosed bleeding are presented in Table 1; crude incidence rates by OAC are presented in Supplementary Table 8. Among ibrutinib + OAC-treated individuals, major bleeding events were predominantly gastrointestinal (n = 3) and cerebral (n = 3) (Supplementary Table 9; additional details on bleed sites/types are presented in Supplementary Tables 10 and 11).

HRs for major and clinically-relevant bleeding could not be estimated because of the low number of events. Ibrutinib + OAC (vs. BR + OAC) had an elevated hazard of provider-diagnosed bleeding (sIPTW-adjusted HR: 2.70, 95% confidence interval [95% CI]: 1.25–5.82) (Table 1 and Supplementary Figure 5). In the DOAC subgroup, the provider-diagnosed bleeding HR for ibrutinib + DOAC (vs. BR + DOAC) was lower than that in the full cohort and statistically compatible with the null (1.91, 0.79–4.64). In the warfarin subgroup, the provider-diagnosed bleeding HR for ibrutinib + warfarin (vs. BR + warfarin) was higher than that in the full cohort (7.33, 2.11–25.48). Sensitivity analysis and effect modification findings are described in Supplemental Results 2.3.

While we were unable to estimate HRs for major and clinically-relevant bleeding, concomitant ibrutinib and OAC treatment was associated with a 2.7-fold hazard of provider-diagnosed bleeding compared to concomitant BR and OAC treatment. This association was notably higher, with a >7-fold hazard, among warfarin-treated individuals. These findings suggest an increased bleeding rate with ibrutinib vs. BR in patients concomitantly treated with OACs, especially warfarin, in clinical practice.

The cumulative incidence of major bleeding among ibrutinib + OAC-treated individuals in our study (1.88%) was lower than that reported in other studies (up to 16%).[5] Potential reasons for this difference are described in Supplemental Discussion 3.1.

Our post-hoc outcome analysis found an elevated rate of provider-diagnosed bleeding with concomitant ibrutinib + OAC vs. concomitant BR + OAC therapy. We calculated a number needed to harm of 6 for provider-diagnosed bleeding in ibrutinib + OAC vs. BR + OAC. Our subgroup analysis revealed a possible differential effect by OAC type, with a higher provider-diagnosed bleeding HR with warfarin than with a DOAC. These findings support previous recommendations to select a DOAC when anticoagulation is warranted, like the occurrence of ibrutinib-related atrial fibrillation, based largely on several serious bleeding cases in patients concomitantly treated with warfarin in an early-phase ibrutinib clinical trial.[1] Despite these previous cautions against using warfarin in ibrutinib-treated individuals, warfarin users accounted for 27% of ibrutinib + OAC-treated individuals in our cohort—with 72% of ibrutinib + warfarin-treated individuals having been on warfarin before starting ibrutinib. It is unclear if these individuals had a specific clinical reason for not switching to a DOAC or if switching was deemed inadvisable due to patient tolerability before ibrutinib initiation. Nonetheless, the notable increased rate of provider-diagnosed bleeding in the warfarin-treated subgroup provides epidemiologic support for the recommendation to use DOACs over warfarin when possible.

We compared major and clinically-relevant bleeding incidence rates to our previous work which, using the same data source and methods, investigated these outcomes in ibrutinib-treated individuals with CLL not concomitantly exposed to OACs.[3] Crude major and clinically-relevant bleeding incidence rates were four times as high for ibrutinib + OAC-treated individuals in this study compared to ibrutinib-treated individuals in the previous study. Further discussion of this comparison is detailed in Supplemental Discussion 3.2.

Our study has limitations. Our provider-diagnosed bleeding post-hoc outcome was based on ICD-9-CM codes from a validated algorithm, but was not validated itself. However, a prior study demonstrated that these codes generally had high sensitivity (93%) and specificity (88%) for identifying physician-diagnosed bleeding from discharge claims.[6] Also, though we adjusted for important confounders, unmeasured confounding may remain. Strengths and additional limitations are described in Supplemental Discussion 3.3.

Because of the multimorbidity of CLL, MCL, and MZL patients and ibrutinib's risk of new-onset atrial fibrillation, clinicians frequently face the conundrum of concomitantly treating patients with ibrutinib and OACs. Our findings suggest an increased provider-diagnosed bleeding rate with ibrutinib vs. BR in patients concomitantly treated with OACs. Thus, consideration of therapies other than ibrutinib may be appropriate in OAC-treated patients. If OAC therapy is necessary for an ibrutinib-treated individual, it may be prudent to consider a DOAC rather than warfarin.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interests

CEL serves on the Executive Committee of and SH directs the University of Pennsylvania's Center for Real-world Effectiveness and Safety of Therapeutics. The Center has received funds to support trainee education from Pfizer and Sanofi. CEL recently received honoraria from the American College of Clinical Pharmacy Foundation, the University of Massachusetts, the University of Florida, and the Consortium for Medical Marijuana Clinical Outcomes Research. CEL receives support for conference travel from John Wiley & Sons. CEL is a Special Government Employee of the United States Food and Drug Administration and consults for their Reagan-Udall Foundation. CEL's spouse is an employee of Merck; neither CEL nor his spouse hold stock in Merck. SH has consulted for the Medullary Thyroid Cancer Consortium (Novo Nordisk, AstraZeneca, and Eli Lilly), Novo Nordisk, Arbor Pharmaceuticals, Biogen MA, Intercept Pharmaceuticals, and Provention Bio, Inc. on matters unrelated to the topic of this paper. JMR has consulted for Pharmacyclics LLC, AbbVie, Genentech, Janssen Pharmaceuticals, BeiGene, AstraZeneca, TG Therapeutics, Verastem Oncology, and SeaGen on matters unrelated to the topic of this paper. JMR's institution has received research funding from LOXO Oncology. AC has served as a consultant for Synergy and New York Blood Center; has received authorship royalties from UpToDate; and his institution has received research support on his behalf from Alexion Pharmaceuticals, Bayer, Novartis, Novo Nordisk, Pfizer, Sanofi, Spark Therapeutics, and Takeda. ND and WY declare no competing interests.

Data Availability Statement

The data that support the findings of these studies are available from Optum Inc., but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available.

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Table 1.

Follow-up time, crude incidence rates, and adjusted outcome findings.

	Ibrutinib + OAC	Bendamustine-Rituximab + OAC
Follow-up time		
Follow-up, sum, in person-years	72	39
Follow-up, median per individual, in days	38	53
Outcomes during follow-up	**N**	
Major Bleeding	9	0
Clinically-relevant Bleeding	19	3
Provider-diagnosed Bleeding	85	14
Measure of outcome occurrence	**Crude Incidence Rate, per 100 person-years (95% Confidence Interval)**	
Major Bleeding	12.5 (6.8 – 23.0)	0 (0 – 0)
Clinically-relevant Bleeding	26.6 (18.1 – 39.1)	7.6 (2.5 – 22.3)
Provider-diagnosed Bleeding	129.1 (105.9 – 157.4)	35.7 (21.4 – 59.8)
Primary Analysis	**Hazard Ratio (95% Confidence Interval)**	
Major Bleeding [*]		
Unadjusted	-	-
Adjusted	-	-
Clinically-relevant Bleeding [*]		
Unadjusted	-	-
Adjusted	-	-
Provider-diagnosed Bleeding		
Unadjusted [†]	3.28 (1.86 – 5.77)	1.00 (reference)
Adjusted [‡§]	2.70 (1.25 – 5.82)	1.00 (reference)
Subgroup Analysis	**Hazard Ratio (95% Confidence Interval)**	
DOAC		
Provider-diagnosed Bleeding [‖¶]	1.91 (0.79 – 4.64)	1.00 (reference)
Warfarin		
Provider-diagnosed Bleeding [‡**]	7.33 (2.11 – 25.48)	1.00 (reference)

DOAC = direct oral anticoagulant; OAC = oral anticoagulant

[*] Unadjusted and adjusted hazard ratios could not be estimated due to low event counts

[†] Did not fail a test for non-proportional hazards (p = 0.99)

[‡] Model weighted based on stabilized inverse probability of treatment weights and adjusted for cohort entry year and household income

[§] Did not fail a test for non-proportional hazards (p = 0.63)

[‖] Model weighted based on stabilized inverse probability of treatment weights and adjusted for cohort entry year, household income, and DOAC dose category at cohort entry. Individuals with a DOAC dose change during follow-up were censored on date of dose change

[¶] Did not fail a test for non-proportional hazards (p = 0.76)

** Did not fail a test for non-proportional hazards (p = 0.32)