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Ibrutinib as a treatment of hematologic autoimmune disorders in patients with indolent B-cell lymphoma

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Abstract

Background: Autoimmune conditions in B-cell lymphomas are frequent. Steroids are standard of care, but many patients require other immunosuppressive agents. Ibrutinib is a Bruton Tyrosine Kinase inhibitor that is approved for B-cell indolent lymphoma treatment. We evaluated the use of ibrutinib in previously treated hematologic immune manifestations associated with B-cell lymphomas.

Results: We conducted a retrospective multicentric observational study. Patients presenting with active, relapsed/refractory B-cell lymphoma associated hematological immune manifestation (autoimmune cytopenia, acquired immune-mediated bleeding disorders) were included. Twenty-five patients were identified. Median age at ibrutinib introduction was 69 years (range 44–84) and median number of previous

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treatment lines before ibrutinib was 2 (1–7). Twenty-two patients (88%) were on concomitant stable treatment at inclusion. Within a median exposure of 8 months (2–35), overall response rate to ibrutinib on immune manifestations was 76% (95% CI, 54.9–90.6); complete response rate 44%. Fourteen patients (63%) were able to be weaned from concomitant treatments. Fourteen patients (56%) presented treatment-related adverse events, mostly Grade 1 or 2.

Conclusions: Ibrutinib in this setting provides good efficacy and safety profile. Clinical trials are needed to define subgroups of patients who will benefit from this strategy and establish its place in the therapeutic arsenal.

KEYWORDS

B-cell lymphoma, hematologic immune disorders, ibrutinib

1 | INTRODUCTION

Autoimmune manifestations associated with B-cell lymphomas are a well-known and frequent event, with an incidence rate of 4%–8% based mostly on retrospective series.[1–3] Such manifestations can occur at any time during the course of the disease, either before B-cell lymphoma onset, at the time of diagnosis or even several years after.[4] Hematologic immune disorders include autoimmune cytopenia such as autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP), immune-mediated neutropenia, pure red cell aplasia, Evans syndrome, or other acquired immune-mediated bleeding disorders. Independently from the natural course of the lymphoma, those conditions can also appear after specific treatment such as targeted therapies[5,6] or purine analogs.[7] Steroids remain the first therapeutic option to treat these manifestations, but many patients become refractory, steroid dependent, or relapse, requiring other treatments such as anti-CD20 or immunosuppressive agents. Efficacy and weaning of such treatments remain uncertain.

Common pathophysiological features exist between autoimmunity and lymphomagenesis, and B-cell receptors seem to play an important role in downstream activation of kinases such as Bruton tyrosine kinase (BTK).[8–10] This enzyme activates intracellular pathways leading to formation of transcriptional factors favoring B-cell development, survival over apoptosis, and immune tolerance breakdown.[11] Ibrutinib is a first-in-class BTK inhibitor approved for treatment of indolent B-cell neoplasms such as chronic lymphocytic leukemia (CLL), Waldenström macroglobulinemia (WM), mantle cell lymphoma (MCL), and marginal-zone lymphoma (MZL). Few studies have described the use of this drug to treat immune conditions associated with lymphoma, mainly case reports or retrospective phase III subgroup analyses.[12–22] Results are promising but focus mostly on CLL patients. Additionally, patients in clinical trials are not representative of routine clinical practice and patients with uncontrolled manifestations are often excluded. Imprecisions regarding previous therapeutic lines and missing safety-related data were noted, limiting the interpretation of the results. To date, only two studies have reported real-life use of ibrutinib as a treatment for refractory hematologic autoimmune condition in patients with CLL, yielding a 58% and 91% overall response rate, respectively, and few adverse events.[6,23] Similar studies concerning the efficacy of ibrutinib to treat hemolysis in secondary cold agglutinin disease (CAD) were also reported.[24]

In this study, we evaluated the efficacy and safety of ibrutinib to treat patients presenting with active refractory/relapsed hematologic immune disorders associated with indolent B-cell lymphomas in routine clinical practice.

2 | METHODS

This retrospective observational study was conducted throughout the national network of the French reference center for adult immune cytopenia (CERECAI), including 12 departments of internal medicine/clinical immunology and clinical hematology, and was conducted in compliance with the Good Clinical Practice protocols and Declaration of Helsinki principles.

2.1 | Study population

Patients aged ≥18 years were eligible if they had a diagnosis of indolent B-cell lymphoproliferation associated with a hematologic immune disorder (isolated or combined autoimmune cytopenia or acquired immune-mediated bleeding syndrome) and at least one prior therapeutic line for immune condition. Other eligibility criteria included ibrutinib introduction for the management of an associated immune disorder. The main exclusion criterion was the introduction of ibrutinib to treat a high-burden tumor.

Diagnoses of lymphoproliferation and associated immune disorder were realized in each center. For immune manifestations, basal characteristics were collected. For AIHA, hemolysis parameters and direct antiglobulin test (DAT) specificity were searched.[25] Data on specific antibodies for ITP and immune-mediated neutropenia were collected whenever available.[26] If needed, bone marrow examination

was performed, especially for thrombocytopenia and neutropenia to be considered as immune-mediated rather than secondary to a bone marrow involvement. Details of prior immunological therapeutic lines, defined by specific therapies to target immune conditions, were assessed. Particular attention to exposure to corticosteroids, anti-CD20, or splenectomy was done. Additionally, stable concomitant therapy was allowed at ibrutinib initiation if necessary.

Concerning tumoral assessment, a basal evaluation (clinical and/or radiological per recommendation) was done and another assessment was performed at the end of observation or in the case of premature arrest of ibrutinib. We decided not to assess cytogenetic and molecular characteristics of each lymphoproliferation because of the heterogeneity of lymphoproliferations.

2.2 | Outcomes

The primary outcome was the assessment of the efficacy of ibrutinib in the treatment of hematologic immune disorder associated with B-cell lymphomas. Overall response rate (complete response [CR] plus partial response [PR]) was the primary endpoint.

As no immune response criteria to ibrutinib were available in the global literature, we created new criteria. CR was defined according to international recommendations[25–28] for each manifestation in the absence of concomitant treatment; PR was defined according to standard recommendations for each manifestation in the absence of associated treatment or if CR criteria were obtained for patients who could not be wean from concomitant treatment. Failure was defined as stable disease, the need to add another immunosuppressive therapy or if CR or PR criteria were not met (Supplemental Tables). Resolution of DAT or disappearance of immune specific antibodies (e.g., antiplatelet antibodies, antigranulocytic inhibitors or FVIII inhibitors) after treatment initiation was assessed per physician discretion.

Secondary outcomes included tumoral response assessment, safety assessment, and treatment weaning for patients with ongoing treatment at ibrutinib initiation. Response criteria for each B-cell lymphoma were in accord with international recommendations for each lymphoproliferation.[29–31]

2.3 | Safety assessment and follow-up

Ibrutinib dose followed standard recommendations (420 mg per day for CLL and WM; 560 mg per day for MZL or MCL) and adaptation was done at the physician's discretion. Safety assessment included evaluation of adverse events (AEs) described in the literature, especially cardiovascular, bleeding, and infectious. Other events were considered significant if they modified the ibrutinib dose or discontinuation. Particular attention was paid to emergent autoimmune cytopenia, a phenomena described after ibrutinib introduction.[5]

Patients were monitored per physician discretion. Patients were censored: at the time of last follow-up (e.g., June 2021); on discontinuation of ibrutinib (reason was documented); or death.

TABLE 1 Baseline demographic and clinical characteristics ($n = 25$)

Demographic characteristics	
Age, years	69 (44–84)
Male sex (%)	17 (68)
Underlying lymphoproliferation (%)	
CLL	18 (72)
WM[a]	4 (16)
MZL[b]	2 (8)
CAD	1 (4)
Binet Stage, for CLL only ($n = 18$)	
A	13 (72)
B	3 (17)
C	2 (11)
Associated Immune condition (%)	
AIHA	15 (60)
ITP	3 (12)
Evans' syndrome	4 (16)
Immune mediated neutropenia	1 (4)
Acquired immune-mediated bleeding disorder	2 (8)
Median time between lymphoproliferation and immune condition diagnosis	
Time for AIHA, months	23 (0–48)
Time for ITP, months	48 (0–64)
Time for Evans syndrome, months	20.5 (2.5–114.5)
Time for autoimmune neutropenia, months	15
Time for acquired immune-mediated bleeding disorder, months	121.5 (69–174)
Prior immunologic therapeutics line (range)	2 (1–7)
Number of systemic therapies for lymphoma, prior to ibrutinib (range)	0 (0–4)
Therapies before ibrutinib (n = 9)	
Fludarabine-based regimens	6 (66)
Bendamustine ± Rituximab	3 (33)
CHOP ± Rituximab	3 (33)
DRC	2 (22)

Note: Values are expressed as median (interquartile range) or numbers (percentage) unless specified otherwise.
Abbreviations: AIHA, autoimmune hemolytic anemia; CAD, cold agglutinin disease; CLL, chronic lymphocytic leukemia; DRC, dexamethasone–rituximab–cyclophosphamide; ITP, immune thrombocytopenia; MZL, marginal zone lymphoma; WM, Waldenström macroglobulinemia.
[a]All Waldenström diseases were considered as stage IV lymphomas according to Ann Arbor classification, due to bone marrow involvement.
[b]One patient with marginal zone lymphoma had an isolated splenic involvement; data were missing for the second patient.

2.4 | Statistical analysis

Categorical variables were expressed as numbers (percentage). Quantitative variables were expressed as median either by IQR (interquartile range) or range. Clinical immune response after treatment with

TABLE 2 Immune characteristics at ibrutinib introduction

Patient	AIC	Lymphoma	Age, years	TTT, montHS[a]	WBC ($\times 10^9$/L)	ANC ($\times 10^9$/L)	ALC ($\times 10^9$/L)	Hb (g/dL)	Plts ($\times 10^9$/L)	FVIII activity, %	WF activity, %	Associated treatment[b]	Immune outcome	Tumoral outcome	Duration,[c] months
1	AIHA	CLL	70	40	46.9	5.1	41.9	6.6	101	/	/	GC	CR	CR	13
2	AIHA	CLL	74	7	4.6	2.7	6	6.2	113	/	/	GC	CR	CR	27
3	AIHA	CLL	61	2	64.9	3.8	60.7	7.6	110	/	/	Rituximab	PR	PR	8
4	AIHA	CLL	63	16	105 000		93	7.0	93	/	/	GC	PR	PR	5
5	AIHA	CLL	69	31	16	2.6	8.2	10.5	190	/	/	GC	CR	PR	5
6	Immune neutropenia	CLL	62	32	1.5	0.3	1.1	10.2	100	/	/	GC	PR	PR	3
7	ITP	WM	84	3	8.2	6.4	0.9	9.7	12	/	/	TPO-RAs	PR	/	8
8	ITP	CLL	73	4	100 000		91	8.0	2	/	/	GC	Failure	PR	2
9	Acquired coagulopathy	CLL	75	14	9.5	8.2	1.1	12.0	216	18	/	GC	CR	CR	25
10	AIHA	CAD	78	23	10.3	7.8	1.3	6.9	541	/	/	Transfusion	Failure	PR	12
11	Acquired coagulopathy	WM	75	68	4.8	3.2	0.8	9.4	212	31	25	/	CR	PR	4
12	AIHA	MZL	79	1	14		12.6	5.4	183	/	/	GC	Failure	CR	2
13	Evans Syndrome	CLL	64	49	60.1	6.6	46.9	8.5	2	/	/	TPO-Ras	PR	SD	10
14	AIHA	MZL	70	336	6.1	3.8	1.2	7.9	236	/	/	Transfusion	Failure	SD	9
15	ITP	MW	69	118	3.2	2.1	0.8	10.8	4	/	/	GC	CR	PR	25
16	AIHA	CLL	68	71	52.4	11.6	45.3	6.0	71	/	/	GC	Failure	SD	2
17	AIHA	CLL	74	5	3.2	0.1	2.2	4.7	29	/	/	Rituximab	PR	PR	10
18	AIHA	CLL	68	35	9.7	6.5	2.5	8.1	240	/	/	/	CR	CR	28
19	Evans Syndrome	WM	67	54	5.2	2.8	1.2	8.7	28	/	/	GC	PR	SD	5
20	Evans Syndrome	CLL	69	29	3.1	1.5	1.1	13.1	6	/	/	TPO-Ras	CR	CR	7
21	AIHA	CLL	44	3	130 000	6	120 000	4.4	182	/	/	/	Failure	PR	2
22	AIHA	CLL	73	30	7.5	1.8	5.6	9.9	165	/	/	Rituximab	CR	CR	24
23	Evans Syndrome	CLL	63	46	28	5.7	21.3	7.1	246	/	/	GC	CR	CR	27
24	AIHA	CLL	70	1	96.4	8.7	84.3	9.5	152	/	/	GC	CR	CR	35
25	AIHA	CLL	76	189	8	3.5	3.5	10.7	86	/	/	Transfusion	PR	CR	8

Abbreviations: AIC, autoimmune condition; AIHA, autoimmune hemolytic anemia; ALC, absolute lymphocytic count; ANC, absolute neutrophilic count; CR, complete response; GC, glucocorticosteroids; Hb, hemoglobin; ITP, immune thrombocytopenia; Plts, platelets; PR, partial response; SD, stable disease; TPO-RAs, thrombopoietin receptor agonists; TTT, time to treatment; WBC, white blood count; WF, Willebrand factor.

[a]Defined by the time between autoimmune condition diagnosis and ibrutinib introduction.

[b]At ibrutinib introduction.

[c]Duration of ibrutinib.

ibrutinib and tumoral response were calculated with exact 95% confidence interval (95% CI) by using Clopper–Pearson method. Data were analyzed using the SAS software version 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

3.1 | Patients

A total of 25 patients were included. Median age at ibrutinib introduction was 69 years (range 44–84 years). Most of the patients were male (17 patients, 68%) (Table 1). We identified mostly CLL (18 patients, 72%), followed by WM (four patients, 16%), two patients with MZL, and one patient with primary cold agglutinin disease (CAD). The majority of patients (16 patients, 64%) had low tumoral burden diseases and were treatment-naive for tumoral condition. Those requiring treatment (nine patients, 36%) received mostly either fludarabin-based regimen or anti-CD20 based regimen.

AIHA was by far the most frequent associated-immune disease ($n = 15$ patients), followed by Evans syndrome ($n = 4$) and ITP ($n = 3$). We also identified one case of immune-mediated neutropenia and two cases of acquired immune-mediated bleeding disorder, one with acquired hemophilia due to an anti-FVIII auto-antibody and one case with acquired von Willebrand disease. Among AIHA, 13 patients had warm AIHA defined by a positive DAT with an IgG or an IgG + C3d positive pattern. Three patients diagnosed with Evans syndrome were revealed by ITP.

Median time elapsed between immune disorder diagnosis and ibrutinib introduction was 30 months and differed for each manifestation. Median number of prior therapies was two (range 1–7). Concerning prior specific immune therapies, 20 patients (80%) received steroids alone; 9 patients (32%) received rituximab monotherapy, and 18 (72%) received rituximab in association, mostly with alkylating agents or steroids. One patient underwent splenectomy (4%). All manifestations were active at inclusion, with relatively severe phenotypes (Table 2). At the time of introduction, 22 patients (88%) were already being receiving a treatment to control the immune manifestation.

Median duration of ibrutinib exposure at time of analysis was 8 months (IQR 5–24). Fourteen patients (56%) discontinued treatment. Reasons for discontinuation included severe AEs (Grade 3/4) in four patients (16%), continuous complete remission in three patients (12%), primary failure in two patients (8%), and relapse in four patients. Median time to relapse was 7.8 months (IQR 4.2–9.7).

3.2 | Efficacy

In this specific population, the overall response rate (ORR) was 76% (95% CI, 54.9–90.6), consisting of 44% with a CR (11 patients) and 32% with a PR (eight patients) using our response criteria (Figure 1A). Among the six failures, three occurred in CLL patients, two in MZL patients, and one in the patient with CAD. Responses according to each autoimmune condition is reported in Figure 1B. For patients who were monitored for the disappearance of antibodies, resolution of DAT occurred in one patient and FVIII inhibitor disappeared for the patient with acquired hemophilia.

Responses did not differ regardless of the number of prior therapeutic lines, steroid response, or anti-CD20 agent response. Naïve-treatment patient for tumoral condition seemed to attain more frequently CR than pre-treated patients (nine patients against two) but ORR were similar (respectively 75% and 77%).

For patients who had concomitant treatment at baseline, 13 could be weaned from this treatment and continued ibrutinib as a monotherapy (62%).

After a median follow-up of 20 months (range 4–64), response was sustained in this relapsed/refractory population, with a median duration of 8 months (IQR 5–24), with long-term response up to 35 months. At the end of observation time, 11 patients (44%) were still pursuing ibrutinib.

For patients with measurable disease, tumoral response was not strictly coincident with immunologic response (Table 2). After

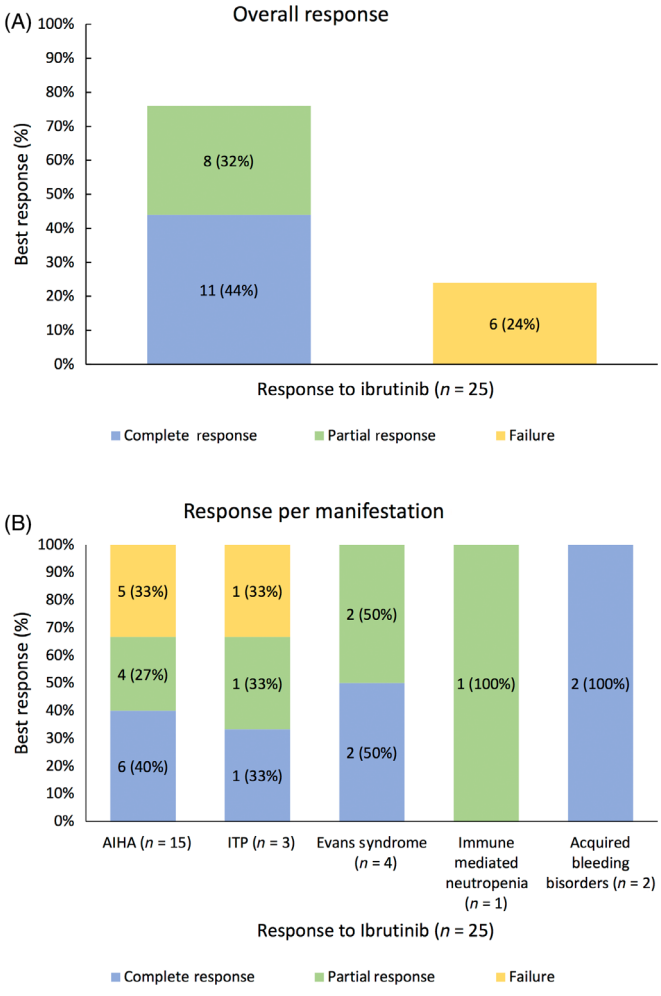

FIGURE 1 Overall response rates to ibrutinib. For all manifestations (A) and according to each manifestation (B). AIHA, autoimmune hemolytic anemia

TABLE 3 Adverse events (AEs) according to grade in all 25 patients

	Any grade[a]	Grade 1	Grade 2	Grade 3 or 4
High blood pressure	3 (12)	0	2 (8)	1 (4)
Atrial fibrillation	2 (8)	0	2 (8)	0
Palpitation	1 (4)	1 (4)	0	0
Hemorrhage	4 (16)	2 (8)	2 (8)	0
Bacterial infection	3 (12)	1 (4)	1 (4)	1 (4)
Viral infection	5 (20)	1 (4)	3 (12)	1 (4)
Fungal infection	1 (4)	0	0	1 (4)
Diarrhea	2 (8)	1 (4)	1 (4)	0
Fatigue	4 (16)	4 (16)	0	0
Cramp	1 (4)	1 (4)	0	0
Neutropenia	3 (12)	0	1 (4)	2 (8)
Thrombocytopenia	1 (4)	1 (4)	0	0

[a]Multiple events may have occurred in several patients.

introduction of ibrutinib, the overall response rate of B-cell lymphoma was 83.3% (IC 95%, 62.6–95.3). 41.7% B-cell lymphoma achieved CR and 41.7% achieved PR ($n = 24$). Among patients with stable disease, two patients had CLL, one patient had WM and one patient had MZL. We did not observe any progressive disease in our cohort.

3.3 | Safety

During treatment period and follow-up, 14 patients (56%) presented at least one treatment related-event (Table 3). Cardiovascular events (high blood pressure, palpitations, or heart rhythm disorders) were found in six patients (24%). Four patients presented bleeding events (16%), with exclusively Grade 1/2 transient bleeding. No discontinuation was observed due to this event and only one occurred in a patient with ITP. Infections occurred in nine patients (36%), mostly due to viral infection in five patients (20%), followed by bacterial infection in three patients (including an endocarditis) (12%), and one fungal event (cerebral aspergillosis) in one. Other adverse events leading to dose reduction or discontinuation were cytopenia and diarrhea with a cumulative incidence of five patients (20%). Discontinuation occurred for four patients (16%), mostly due to infectious related event (three patients) and one patient with diarrhea (one patient).

We did not observe any case of emergent autoimmune cytopenia due to ibrutinib in our cohort.

One death due to pneumonia was reported during follow-up, but the referring physician did not consider it to be related to the treatment.

4 | DISCUSSION

Relapse and refractory primary or secondary immune disorders remain a therapeutic challenge. Concerning immune disorders associated with B-cell lymphomas, relapse may affect the natural course of the disease and can lead to reduced quality of life or even death, independently of tumor progression. Ibrutinib is a BTK inhibitor developed to treat B-cell indolent lymphoproliferation, initially CLL[32] then subsequently WM,[33] MCL,[34] and MZL.[35] It is an interesting alternative to other regimens and to chemoimmunotherapy, which can lead to toxicities in these populations.

In this multicenter study, we sought to evaluate the efficacy and safety of ibrutinib in B-cell neoplasms associated with hematologic immune disorders. To date, few data support the use of ibrutinib in this setting.[6,12–24] Here, we report real-world use of ibrutinib in the treatment of active, refractory/relapsed hematologic immune conditions associated with various B-cell neoplasms. It is also one of the first description of ibrutinib used for the treatment of acquired hemophilia and acquired von Willebrand disease.

Demographic characteristics of our population were on par with the literature and lymphoproliferation in our cohort focused not only on CLL but also on WM, MZL, and CAD. Immune manifestation distribution was atypical, with a low rate of ITP which can partially be explained by a selection bias due to the putative bleeding risk of ibrutinib. All patients presented with a refractory/relapsing associated immune disease, defined by the failure of at least one prior therapeutic line, with a median rate of two (up to seven therapeutic lines). All manifestations were active at inclusion, either with persistent cytopenia or the need of additional treatment.

Our study showed a 76% ORR with 44% of CR (95% CI, 54.9–90.6). Those rates are not inferior to those found in the literature, which concerned mostly CLL patients and patients with either active or past manifestations. Among non-responders, three patients were diagnosed with CLL, two with MZL, and one with CAD. We cannot draw conclusions concerning efficacy for MZL and CAD patients, but it is our opinion that BTK inhibitor in MZL patients seems to be less effective as a single agent concerning tumoral condition and may be less dependent on the BTK pathway for survival or autoimmunity.[35] Concerning CAD, promising results are emerging as shown by Jalink et al.[24] In a cohort of 10 patients, who obtained one PR and nine CRs with transfusion independence and low-grade complications after a follow-up of 20 months. In our study, among patients receiving a

treatment before ibrutinib initiation ($n = 22$), 13 could be weaned from the associated treatment (62%), which suggests a steroid or immunosuppressive-sparing role of ibrutinib. Also, response was sustained for this refractory population with a median duration of response of 8 months, including long-term responses (up to 35 months).

We realized that the tumoral response and the immunological response were not strictly identical. This could be explained by several hypotheses. First, clonal evolution may drive evolutionary pressure linked to prior therapies with the emergence of multiples clones. For example, in CLL, it could be demonstrated that immune disorders tend to appear in patients with high cytogenetic or molecular risks (non-mutated IgVH status, TP53 mutation) or exposure to anterior chemoimmunotherapy such as purine analogs.[7,36,37] However, we decided not to study cytogenetic and molecular characteristics because of the heterogeneity of our population, preventing verification of this hypothesis. Also, BTK inhibitors have an action targeted not only on B cells but also on micro-environment cells such as T cells and macrophages. It could be demonstrated that patients with B-cell neoplasms and immune disorders had perturbations in T-cell subsets, notably on T regulatory cells and T helper cells (Th17).[38,39] Ibrutinib, by inhibiting intracellular T cells kinases in whose structure is close to BTK (e.g., SYK, ITK) can select proliferation of T cells with a Th1 profile over those with a Th17 profile, which favors immune tolerance and tumoral defense. These observations suggest that ibrutinib, and BTK inhibitors more generally, may not be limited to autoimmune phenomena associated with B-cell neoplasms but could be used in primary autoimmune cytopenia or immune disorders associated with systemic diseases.[40,41]

In our study, safety profiles of cardiovascular, infectious, and hemorrhagic events were similar to what has been previously reported. It is interesting to note that infectious events were mostly a result of reactivation of the herpes virus, but we also report Grade 3 hepatitis, infectious endocarditis, and cerebral aspergillosis which occurred in the neutropenic patient. Although rare, those events are important to consider because of underlying immunodepression due to prior therapeutic lines such as corticotherapy, immunosupressive agents, or a specific background. Specific prophylaxis should be started depending on the patient, with mandatory antiviral prophylaxis as recommended.

Another interesting point is that only four patients presented with hemorrhagic events considering that we had four patients treated for ITP, three for Evans syndrome with thrombocytopenia, and two for acquired bleeding disorders. These events occurred only in one patient with thrombocytopenia and were mostly low-grade cutaneo-mucosal bleeding and none of these events led to discontinuation. Finally, we did not observe any emergent autoimmune cytopenia after ibrutinib introduction. This specific event has a variable incidence of 1%–6% among different series[5,6,23] and can be found not only for ibrutinib but also for other targeted therapies such as BCL2 inhibitors or PI3K inhibitors. It is important to detect this event because it can modify the natural history of immune conditions and can have a non-negligible impact, such as the management of targeted therapy. However, this data is limited because of the size of our cohort and a potential selection bias.

Several limitations must be pointed out. Besides the size of the cohort, our study is retrospective which may limit the results. We also decided not to collect intrinsic characteristics of lymphomas because of our population's heterogeneity, which can be another source of bias. For example, TP53 deletion in CLL could unconsciously guide a clinician to treat the patient with ibrutinib, independently of other variables.

To date, there is no clearly defined indication for ibrutinib in the management of secondary immune manifestations in clinical routine practice. In our opinion, regular immunosupressive treatment, as recommended per specific institution standard of care should be followed. Ibrutinib should be considered in cases of complications of immunosuppressive agents, absence of other available therapies available and/or in the case of predominant active B-cell lymphoma with hematologic immune conditions. Ibrutinib as a weaning therapy may also be considered.

To conclude, ibrutinib as a treatment for refractory/relapsing hematologic immune disorders associated with B-cell indolent lymphoproliferation seems to be an interesting and novel strategy to control both tumoral and immune condition with a relatively safe tolerance profile. Therapeutic applications may be even wider, with potential indication in primary autoimmune cytopenia, for example. Prospective studies including these specific populations should be planned to confirm these data, to investigate predictive factors of response, and to define the exact place of this strategy in clinical practice.

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AUTHOR CONTRIBUTIONS

Adrien Daniel and Louis Terriou designed the study, wrote the paper and analyzed the data. Adeline Pierache made the statistical analysis. All authors revised critically, approved the manuscript, and contributed significantly to the work.

CONFLICT OF INTEREST

David Ghez received research grant for Janssen. Charles Herbaux declares conflict of interest with Janssen. No other potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available within the article and its Supplementary Materials. We present here the use of ibrutinib as a treatment of relapsed/refractory hematologic immune disorders associated to various B-cell lymphoma, not only focusing on chronic lymphocytic leukemia, and in a real-life experience. Ibrutinib as a single agent in this feature was associated with interesting response rate (ORR 76%, CR 42%) with acceptable tolerance. In our opinion, this treatment can be an interesting option in case of

complications to immunosuppressive agents or in the absence of other available therapy agents, even if our results should be confirmed in wider and prospective studies.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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