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Original Article

Incidence and associated risk factors for invasive fungal infections and other serious infections in patients on ibrutinib

Thomas Holowka [a,*], Harry Cheung [b], Maricar Malinis [c], Geliang Gan [d], Yanhong Deng [d], Sarah Perreault [e], Iris Isufi [f], Marwan M. Azar [g]

[a] Department of Internal Medicine, Yale School of Medicine, 333 Cedar St, New Haven, CT, 06510, USA
[b] Yale School of Medicine, 367 Cedar St, New Haven, CT, 06510, USA
[c] Section of Infectious Disease, Department of Internal Medicine, Yale School of Medicine, USA
[d] Yale Center for Analytical Science, Yale School of Public Health, PO Box 208034, New Haven, CT, 06520, USA
[e] Department of Pharmacy, Yale New Haven Health, 20 York St, New Haven, CT, 06510, USA
[f] Section of Hematology, Department of Internal Medicine, Yale School of Medicine, 333 Cedar St, New Haven, CT, 06510, USA
[g] Section of Infectious Disease, Department of Internal Medicine, Yale School of Medicine, 333 Cedar St, New Haven, CT, 06510, USA

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ABSTRACT

Background: Ibrutinib is a small molecule tyrosine kinase inhibitor that blocks the activity of B cells and other immune effectors and is used in a variety of hematologic malignancies. There have been numerous reports of increased frequency of serious infections including invasive fungal infections (IFI) in patients on ibrutinib.
Methods: Demographic and clinical features of all patients receiving ibrutinib at a single tertiary care center were collected from electronic medical records. Univariate and multivariate statistical analyses were performed to find out the factors associated with infection.
Results: A total of 244 patients received ibrutinib for hematologic malignancies, of which 44 (18.0%) experienced $\geq$ 1 serious infection including 5 (2.0%) with IFI (1 pulmonary cryptococcosis, 4 pulmonary aspergillosis), 39 (16.0%) with bacterial infections and 8 (3.3%) with viral infections. Ten patients (4.1%) experienced multiple infections or co-infections while on ibrutinib and 10 (4.1%) expired or were transferred to hospice as a result of infection. In multivariate analysis risk factors that were less common in uninfected versus infected patients included advanced age (73 years vs. 77 years), Eastern Cooperative Oncologic Grade (ECOG) performance score $\geq$ 2 (6.5% vs. 31.8%) and concurrent use of steroids (4.5% vs. 20.5%) or other cytotoxic agents (0% vs. 4.6%).
Conclusions: There was a high rate of serious infection but relatively few IFI in patients receiving ibrutinib. Most patients who developed serious infections while on ibrutinib had additional predisposing risk factors including concurrent use of steroids or other cytotoxic agents, advanced age and frailty.

1. Introduction

Ibrutinib is a small molecule inhibitor that targets Bruton's tyrosine kinase (BTK) and blocks signaling downstream of the B-cell receptor, leading to reduced B-cell activation [1]. Ibrutinib and other small molecule kinase inhibitors have been proposed as groundbreaking therapies due to their specific mechanism of action and reduced toxicity [2]. Ibrutinib was first approved for chronic lymphocytic leukemia (CLL) in 2013 and has subsequently been approved for various Non-Hodgkin Lymphomas (NHLs) including Waldenstrom's Macroglobulinemia (WM), Mantle Cell Lymphoma (MCL) and Marginal Zone Lymphoma as well as Graft Versus Host Disease (GVHD) in allogeneic hematopoietic stem cell transplant (HSCT) [3,4]. It is now recommended as first line therapy in certain variants of CLL and several forms of NHL including WM due to its efficacy and safety profile [4–6].

Ibrutinib is generally considered less immunosuppressive than other chemotherapeutic regimens by virtue of its targeted mechanism and was even suggested to help reconstitute humoral immunity and protect against infection [7]. However, early clinical studies documented an increased risk of infection, including upper respiratory tract infection, pneumonia, cellulitis and sepsis [4,8,9]. More recently, numerous case reports and series have suggested an increased risk of invasive fungal

* Corresponding author.
E-mail addresses: thomas.holowka@unchealth.unc.edu (T. Holowka), harry.cheung@yale.edu (H. Cheung), maricar.malinis@yale.edu (M. Malinis), geliang.gan@yale.edu (G. Gan), yanhong.deng@yale.edu (Y. Deng), sarah.perreault@ynhh.org (S. Perreault), iris.isufi@yale.edu (I. Isufi), marwan.azar@yale.edu (M.M. Azar).

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infections (IFI) due to *Cryptococcus*, *Aspergillus*, *Fusarium,* fungi of the order Mucorales, *Pneumocystis jirovecii* and *Histoplasma* [3,8,10–13]. In contrast to early clinical trials which reported rates of IFI between 0 and 3.2% in patients on ibrutinib, a phase 1b study of 18 patients with primary CNS lymphoma treated with ibrutinib reported a 44% incidence of IFI including several with central nervous system (CNS) aspergillosis, with the major caveat that these patients also received chemotherapy and dexamethasone concurrently [3,8,10,14–16]. A recent retrospective, single-center study of patients who received ibrutinib found that 11.4% experienced serious infections, defined as those requiring hospitalization or parenteral therapy, including 4.2% who experienced IFI [17]. A separate single center study found a 2.5% incidence of IFI in CLL patients on ibrutinib, which was higher than was expected for this population [18].

The individual contribution of ibrutinib to the risk of serious infections and IFI is unclear. Several studies suggest that this risk is compounded by the presence of additional risk factors such as concurrent steroid use, neutropenia, and prior or concurrent chemotherapy [13,14,17,18]. However there have been multiple reports of IFI in patients initiated on ibrutinib with hematologic malignancy as their only evident risk factor [7,17,19,20]. In order to clarify the impact of BTK inhibition in patients with hematologic malignancies, we aimed to determine the incidence of IFI and other serious infections in all patients who received ibrutinib at a single tertiary academic center and further characterize associated risk factors of infection.

2. Materials and methods

2.1. Data collection

In order to determine the incidence of serious infections and associated risk factors for infection in patients on ibrutinib, a retrospective review of electronic medical records was performed, as approved by the Yale University Institutional Review Board (protocol # 2000025831). Patients ≥18 years of age who received ibrutinib for a minimum duration of 7 days between July 1, 2014 and July 1, 2019 were included. Patients receiving ibrutinib for treatment of GVHD were excluded.

Demographic and clinical data were recorded from time of initiation of ibrutinib until either death, discontinuation of ibrutinib, or last known contact prior to July 1, 2019 (whichever occurred first). These included age at time of initiation of ibrutinib, sex, race, ethnicity, ibrutinib treatment duration (in weeks), ibrutinib dose, hematologic malignancy diagnosis, number of prior chemotherapy regimens and prior HSCT. Eastern Cooperative Oncologic Group (ECOG) performance score (a measure of functional status on a scale of 0–5), the occurrence of neutropenia or lymphopenia (absolute neutrophil count ≤ 500 per microliter or absolute lymphocyte count ≤ 400 per microliter on at least 2 separate measurements on separate days), hypogammaglobulinemia (defined as IgG ≤ 700 mg/dL requiring treatment with intravenous immunoglobulin), anti-fungal prophylaxis, *anti-Pneumocystis* prophylaxis, or anti-bacterial prophylaxis following initiation of ibrutinib were also recorded. Additionally concurrent treatment with steroids at a dosage of ≥0.3 mg/kg prednisolone or its equivalent for ≥3 weeks or with cytotoxic agents affecting T-cell proliferation within 90 days of treatment with ibrutinib was recorded in accordance with the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium definition for agents that confer increased risk for IFI [21].

Occurrence of bacterial, viral, or fungal infection was determined based on the diagnosis documented in the medical record and confirmed by review of appropriate supporting imaging, microbiology, histopathology, or other diagnostic markers. The definitions of pneumonia, urinary tract infection and skin and soft tissue infections were based on Infectious Diseases Society of America guidelines; other infections were defined using Centers for Disease Control and Prevention criteria [22–25]. Invasive fungal infections were defined using consensus definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium, and any proven or probable IFI was deemed a serious infection [21]. Otherwise, serious infections were defined as those requiring of hospitalization and/or parenteral antibiotic treatment, consistent with other studies of infections in patients on ibrutinib [10,17].

2.2. Statistical analyses

Data were represented as medians (with range) for continuous variables or percentage of total (with count) for categorical variables. To evaluate the risk factors of serious infection, univariate Cox's proportional hazards regression models were built. Variables with p value less than 0.05 were considered as candidate variable for multivariate Cox's proportional hazards regression model. The Akaike information criterion (AIC) was used to choose the final best fit model. Time to infection was defined as from the day of the initiation of ibrutinib to the day of infection or last follow up date. Data was censored at last follow date if no infection occurred. The proportional hazards assumption was checked using graphical diagnostics based on the scaled Schoenfeld residuals. Cumulative incidence of infection was determined by dividing the number of patients that had experienced at least one infection of any kind, at least one bacterial infection, at least one viral infection, or at least one IFI by the total number of patients in the cohort (244) at each week since initiation of ibrutinib, as depicted in Fig. 1. P value less than 0.05 was considered as statistically significant. All analyses were completed in SAS (version 9.4; Cary, NC) and figures were created using Graphpad Prism software (version 9.02; San Diego, CA).

3. Results

3.1. Patient characteristics

A total of 244 patients met the inclusion criteria. The median age at initiation of ibrutinib was 73 years (range 32–98) and the patient population was 60.2% (n = 147) male and 88.2% (n = 216) Caucasian. The majority of patients received ibrutinib for treatment of CLL (64.8%, n = 158), with the remainder receiving ibrutinib for WM (14.3%, n = 35), MCL (8.2%, n = 20), or another NHL (12.7%, n = 31). The median duration of ibrutinib treatment was 50 weeks (range: 1–354 weeks). Most patients (79.5%, n = 194) received an ibrutinib dose of 420 mg, with 9.8% (n = 24) receiving an ibrutinib dose of 560 mg. Regarding chemotherapy exposure prior to ibrutinib, 30.7% (n = 75) of patients had not received prior chemotherapy whereas 14.3% (n = 35) had received ≥3 prior chemotherapy regimens. Most chemotherapy regimens involved rituximab alongside an alkylating agent such as bendamustine, fludarabine or cyclophosphamide, with many patients also having received an antimetabolite such as cytarabine or fludarabine or

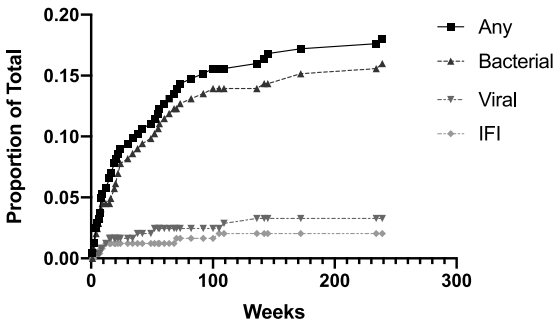

Fig. 1. Incidence of Serious Infection. Proportion of patients experiencing ≥1 infection from bacterial, viral, invasive fungal (IFI) or any organism.

another chemotherapeutic agent. During ibrutinib treatment, 11.1% (n = 27) had an ECOG performance score of ≥2, 7.8% (n = 19) had neutropenia, 11.5% (n = 28) had lymphopenia, and 4.9% (n = 12) had received a prior HSCT. Among patients receiving ibrutinib during the study period, 7.4% (n = 18) received concurrent steroids and 0.8% (n = 2) received additional cytotxic agents concurrently, one receiving cytarabine and the other bendamustine. Additionally, 2.9% (n = 7) received anti-bacterial prophylaxis, 1.6% (n = 4) received anti-fungal prophylaxis and 4.5% (n = 11) received *anti-Pneumocystis* prophylaxis. Patient demographic and clinical features are summarized in Table 1.

3.2. Serious infection in patients on ibrutinib

Among 244 total patients on ibrutinib, 44 (18.0%) developed at least 1 serious infection, requiring hospitalization and/or parenteral antibiotic treatment during the study period. Of the patients who developed a serious infection, 5 developed an IFI (2.0% of all patients), 39 developed ≥1 serious bacterial infection (15.9% of all patients) and 8 ≥ 1 serious viral infection (3.3% of all patients) (Table 1). Ten patients (4.3% of all patients) experienced at least 2 serious infections or co-infections, amounting to a total of 68 infections among all patients. Most infections occurred within 1 year of initiation of ibrutinib, with a median of 27 weeks on ibrutinib prior to first infection (Fig. 1). Most infections occurred in patients receiving ibrutinib alone (81.8%, n = 36); 11.4% (n = 5) occurred in patients on concurrent steroids and 2.3% (n = 1) occurred in patients on additional cytotoxic therapy concurrently. In terms of anti-microbial prophylaxis, only 1 bacterial infection was recorded in a patient on anti-bacterial prophylaxis (2.3), and no IFI were recorded on anti-fungal prophylaxis. Ibrutinib was ultimately continued after resolution and recovery of most infections, and stopped permanently in only 5 patients who recovered from infection. Ten patients expired or were transferred to hospice as a result of an infection, representing 22.7% of all patients who were infected and 4.1% of the entire cohort on ibrutinib. Features of patients at a time of infection and outcome of infection are summarized in Table 2.

3.2.1. Fungal infections

There was a total of 5 IFI in 5 patients, all of which were fungal pneumonias. These included 1 patient with pulmonary cryptococcosis proven by pathology from pleural fluid and 4 patients with probable invasive pulmonary aspergillosis. Of the 4 cases of pulmonary aspergillosis, 3 had positive culture from bronchoalveolar lavage and/or sputum and one had elevated galactomannan of 6.96 (and beta-D glucan >500 pg/ml) along with corroborating imaging and clinical presentation. There were no cases of CNS fungal infection based on review of head imaging and recorded neurologic exam nor were there any cases of *Pneumocystis jirovecii* pneumonia. Additional information about patients experiencing IFI in this cohort is included in Table 3.

3.2.2. Bacterial infections

There were 53 serious bacterial infections among 39 patients. The most common infectious syndromes were pneumonia (n = 20), urinary tract infection (n = 13) and skin and soft tissue infection (n = 8), bacteremia of unknown source (n = 4), *Clostridioides difficile* colitis (n = 3), bacterial endocarditis (n = 2), cholecystitis (n = 1), septic arthritis (n = 1) and Lyme meningoencephalitis (n = 1). The most frequently identified causative bacteria were *Escherichia coli* (n = 10), *Staphylococcus aureus* (n = 10) and *Pseudomonas aeruginosa* (n = 9), with an additional 12 infections where no organism was identified; these were diagnosed based on clinical criteria (see Table 2).

3.2.3. Viral infections

There were 10 serious viral infections among 8 patients (Table 2). The clinical syndromes included pneumonia (n = 8) caused by rhinovirus (n = 4), human metapneumovirus (n = 3) and parainfluenza virus; and disseminated herpes zoster caused by varicella zoster virus (n = 2).

3.3. Identification of risk factors for serious infection

Characteristics of patients experiencing serious infections are listed in Table 4. These were compared to those who did not experience a serious infection. Univariate statistical analysis comparing uninfected versus infected patients demonstrated significant differences in age, with hazard of infection increased by 4% if patient was 1 year older (p = 0.01); ECOG performance score, with hazard of infection in patients with a score <2 reduced by 82% compared with those with ECOG performance score ≥2 (p < 0.001); cancer diagnosis, with hazard of infection in patients diagnosed with CLL reduced by 53% compared with

Table 1
Baseline characteristics of patients on ibrutinib. Expressed as percentage of total with absolute number in parentheses, except where medians listed with range in parentheses. * = 6 diffuse large B cell lymphoma (DLBCL), 6 marginal zone lymphoma (MZL), 4 lymphocytic lymphoma, 3 follicular lymphoma, 2 primary CNS lymphoma (PCNSL), 1 lymphoid granulomatosis, 9 prolymphocytic/undefined. ** = 1 DLBCL, 1 MZL, 1 PCNSL, 3 prolymphocytic/undefined. CLL = chronic lymphocytic leukemia, ECOG = Eastern Cooperative Oncologic Group, GVHD = graft versus host disease, HSCT = hematopoietic stem cell transplant, WM = Waldenstrom's Macroglobulinemia, MCL = Mantle Cell Lymphoma, NHL = Non-Hodgkin Lymphoma, WM = Waldenstrom's Macroglobulinemia.

Characteristic	Total (n = 244)	CLL (n = 158)	WM (n = 35)	MCL (n = 20)	Other NHL (n = 31)*
Median Age (Years)	73 (32–98)	73 (32–97)	74 (52–95)	77 (61–87)	79 (42–98)
Median Weeks on Ibrutinib	50 (1–354)	58 (1–270)	65 (3–354)	32 (1–238)	30 (2–216)
Male Sex	60.2 (147)	62.7 (99)	65.7 (23)	70 (14)	35.5 (11)
Caucasian	88.2 (216)	88.6 (140)	85.7 (30)	90 (18)	90.3 (28)
ECOG ≥2	11.1 (27)	5.1 (8)	11.4 (4)	30 (6)	29.0 (9)
No Prior Cancer Treatment	30.6 (75)	34.2 (54)	31.4 (11)	5 (1)	29.0 (9)
1 to 2 Prior Cancer Regimens	54.9 (134)	56.3 (89)	51.4 (18)	70 (14)	41.9 (13)
≥3 Prior Cancer Regimens	14.3 (35)	9.5 (15)	17.1 (6)	25 (5)	29.0 (9)
Ibrutinib Dose of 560 mg	9.8 (24)	2.5 (4)	0 (0)	70 (14)	19.3 (6)
Concurrent Cytoxic Agents	0.8 (2)	0.6 (1)	0 (0)	5.0 (1)	0 (0)
Concurrent Steroids	7.3 (18)	5.1 (8)	5.7 (2)	15 (3)	16.1 (5)
Neutropenia	7.8 (19)	8.2 (13)	5.7 (2)	15 (3)	3.2 (1)
Lymphopenia	11.4 (28)	7 (11)	11.4 (4)	25 (5)	25.8 (8)
Prior HSCT	4.9 (12)	0	2.9 (1)	35 (7)	12.9 (4)
Hypogammaglobulinemia	22.5 (55)	24.1 (38)	28.6 (10)	25.0 (5)	6.5 (2)
Anti-bacterial Prophylaxis	2.9 (7)	3.2 (5)	2.9 (1)	5 (1)	0 (0)
Anti-fungal Prophylaxis	1.6 (4)	0.6 (1)	5.7 (2)	5 (1)	0 (0)
Anti-Pneumocystis Prophylaxis	4.5 (11)	4.4 (7)	5.7 (2)	5 (1)	3.2 (1)
Total Infection	18.0 (44)	15.2 (24)	11.4 (4)	50 (10)	19.4 (6)**
Bacterial Infection	15.9 (39)	13.9 (22)	8.6 (3)	40 (8)	19.4 (6)**
Viral Infection	3.3 (8)	2.5 (4)	5.7 (2)	10 (2)	0 (0)
Invasive Fungal Infection	2 (5)	1.3 (2)	0 (0)	15 (3)	0 (0)

Table 2
Characteristics of patients at the time of infection and outcomes. Expressed as percentage of total with absolute numbers in parentheses except where medians listed with range in parentheses. Any infection columns include recurrent infections and co-infections in addition to the first infection.

	First Infection (n = 44)	Any Infection (n = 68)	Any Bacterial Infection (n = 53)	Any Viral Infection (n = 10)	Any Invasive Fungal Infection (n = 5)
Median Age (Years)	77 (49–95)	77 (49–95)	78 (49–95)	65 (60–86)	73 (66–86)
Median Weeks on Ibrutinib	27 (1–239)	41 (1–310)	42 (2–310)	45 (1–234)	15 (4–105)
Concurrent Steroids	11.4 (5)	14.7 (10)	15.1 (8)	10 (1)	20 (1)
Concurrent Cytotoxic Agents	2.2 (1)	2.9 (2)	0 (0)	10 (1)	20 (1)
Anti-bacterial Prophylaxis	2.2 (1)	1.5 (1)	1.9 (1)	0 (0)	0 (0)
Anti-fungal Prophylaxis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
***Anti-Pneumocystis* Prophylaxis**	0 (0)	11.8 (8)	9.4 (5)	20 (2)	20 (1)
Survived, Ibrutinib Stopped	6.8 (3)	7.4 (5)	9.4 (5)	0 (0)	0 (0)
Survived, Recurrent Infection	18.2 (8)	29.4 (20)	22.1 (15)	40 (4)	20 (1)
Expired/Hospice	15.9 (7)	14.7 (10)	15.1 (8)	0 (0)	40 (2)

Table 3
Individual characteristics of each patient with Invasive Fungal Infections (IFI) at time of infection. ** = Cytarabine. CLL = chronic lymphocytic leukemia, ECOG = Eastern Cooperative Oncologic Group, HSCT = hematopoietic stem cell transplant, MCL = Mantle Cell Lymphoma.

	IFI Patient 1	IFI Patient 2	IFI Patient 3	IFI Patient 4	IFI Patient 5
	Pulmonary cryptococcosis	Pulmonary aspergillosis	Pulmonary aspergillosis	Pulmonary aspergillosis	Pulmonary aspergillosis
Age	77	68	66	73	86
Male sex	Yes	Yes	No	Yes	Yes
Caucasian	Yes	Yes	Yes	Yes	Yes
ECOG	3	0	1	2	Unknown
Cancer diagnosis	MCL	CLL	MCL	CLL	MCL
# of Prior Cancer Regimens	1	0	2	0	1
Weeks on Ibrutinib	70	15	8	4	155
Ibrutinib Dose (mg)	560	420	560	280	420
Concurrent Cytotoxic Agents	No	No	Yes**	No	No
Concurrent Steroids	No	No	Yes	Yes	No
Neutropenia	No	No	No	No	No
Lymphopenia	No	No	No	No	No
Prior HSCT	No	No	Yes	No	No
Hypogamma-globulinemia	No	No	No	No	Yes
Anti-bacterial Prophylaxis	No	No	No	No	No
Anti-fungal Prophylaxis	No	No	No	No	No
Anti-Pneumocystis Prophylaxis	No	No	No	No	No

Table 4
Comparison of uninfected versus infected patients on ibrutinib. Expressed as percentage of total with absolute numbers in parentheses except where medians listed with range in parentheses. Hazard ratios (HR) expressed in terms of uninfected vs. infected for categorical variables or for every increase by a unit of 1 for continuous variables. CLL = chronic lymphocytic leukemia, ECOG = Eastern Cooperative Oncologic Group, GVHD = graft versus host disease, HSCT = hematopoietic stem cell transplant, ND = Not Done, NHL = Non-Hodgkin Lymphoma.

Characteristics	Uninfected (n = 200)	Infected (n = 44)	Comparison	HR (95% CI), Univariate	P value, Univariate	HR (95% CI), Multivariate	P value, Multivariate
Median Age (Years)	73 (32–98)	77 (51–95)	Increase by 1	1.04 (1.01–1.07)	0.01	1.04 (1.01–1.07)	0.022
Male sex	58.5 (117)	68.2 (30)	Male vs. Female	0.74 (0.39–1.39)	0.35	ND	ND
Caucasian	89.0 (178)	86.4 (38)	Caucasian vs. Other	0.77 (0.32–1.82)	0.55	ND	ND
ECOG ≥2 or greater	6.5 (13)	31.8 (14)	<2 vs. ≥2	0.18 (0.09–0.34)	<0.001	0.25 (0.12–0.51)	0.002
NHL	32.5 (65)	47.7 (21)	CLL vs. NHL	0.47 (0.26–0.87)	0.01	ND	ND
Ibrutinib Dose 560 mg	7.5 (15)	20.5 (9)	<560 vs. 560	0.35 (0.17–0.73)	0.01	ND	ND
Concurrent Cytotoxic Agents	0 (0)	4.6 (2)	No vs. Yes	0.1 (0.02–0.42)	0.002	0.08 (0.02–0.37)	0.001
Concurrent Steroids	4.5 (9)	20.5 (9)	No vs. Yes	0.24 (0.12–0.51)	<0.001	0.36 (.16–0.80)	0.012
Neutropenia	5.5 (11)	18.2 (8)	No vs. Yes	0.33 (0.15–0.71)	0.005	0.60 (0.25–1.45)	0.26
Lymphopenia	9.5 (19)	20.5 (9)	No vs. Yes	0.55 (0.26–1.15)	0.11	ND	ND
Prior HSCT	4.0 (8)	9.1 (4)	No vs. Yes	0.41 (0.15–1.14)	0.09	ND	ND
Hypogamma-globulinemia	20.5 (41)	31.8 (14)	No vs. Yes	0.75 (0.40–1.42)	0.38	ND	ND

those diagnosed with NHL ($p = 0.01$); ibrutinib dose, with hazard of infection in patients on lower dose (<560 mg) reduced by 65% ($p = 0.01$); concurrent steroid use, with hazard of infection in patients without concurrent steroid use reduced by 76% ($p < 0.001$); concurrent cytotoxic agents, with hazard of infection in patients without concurrent cytotoxic agents reduced by 90% ($p = 0.002$); and neutropenia, with

hazard of patients without neutropenia reduced by 67% ($p = 0.005$). In multivariate analysis, age, ECOG performance score and concurrent steroid or other cytotoxic agent use remained significantly reduced in uninfected versus infected patients.

4. Discussion

In this single-center retrospective study, the incidence of one or more serious infections in patients with hematologic malignancies receiving ibrutinib therapy was 18.0%, with the majority (16.1%) being bacterial in nature, 4.3% experiencing multiple infections and 4.1% expiring or transferring to hospice due to their infection. These results are consistent with those of another single center study which reported an overall incidence of serious infection of 11% in patients with hematologic malignancies on ibrutinib [17]. Notably, only 11.4% of serious infections occurred in patients receiving concurrent steroids. Collectively, these findings suggest that patients with hematologic malignancies who receive ibrutinib are at increased risk of serious infection but whether this risk can be attributed to ibrutinib alone or is primarily due to other co-occurring risk factors is unclear.

The impact of ibrutinib on the immune system is likely to extend beyond its ability to block B-cell activation downstream of BTK, as recent studies have revealed a role for BTK in the activation of macrophages, neutrophils and dendritic cells during infection [26–29]. The inhibition of BTK in innate immune effectors, as well as off-target inhibition of other kinases, have been proposed as the basis for broader ibrutinib-related immunosuppressive effects than initially proposed, with implications for the risk of infections [28,30,31]. Of note, IFI are extremely rare in pediatric patients with X-linked agammaglobulinemia (XLA) who lack functional BTK [14,32–34]. This observation suggests that BTK inhibition alone via ibrutinib may be insufficient to predispose an individual to IFI and that other risk factors related to underlying hematologic malignancy may account for increased susceptibility to IFI.

Only 2% of patients in our cohort experienced a proven or probable IFI, which was only slightly lower than the incidence recorded in two other single center studies, one of which reported incidence of 4% in all patients on ibrutinib and another which found incidence of 2.5% in CLL patients on ibrutinib. Notably, these rates are similar to the reported incidence of IFI (0.5–4%) in patients with hematologic malignancies in the absence of ibrutinib [17,18,35–37], suggesting that ibrutinib alone may not significantly increase the risk of IFI. However, cases of IFI in patients on ibrutinib without other clear risk factors have been reported [7,17,19,20]. In our study, 2 of 5 patients who experienced IFI had other risk factors for fungal infections including steroid use (with one of these additionally on cytarabine) while a third was advanced in age (86 years) and a fourth had poor functional status (ECOG 3). Only one patient had no clear risk factors besides their underlying disease (Table 3).

Prior studies had suggested an increased risk of CNS aspergillosis on ibrutinib, however there were no such cases among our cohort [13,14,19]. The most common infectious syndrome in our population was pneumonia due to bacterial and viral pathogens. Both community acquired and opportunistic pathogens were detected, illustrating the susceptibility of this immunosuppressed population to a wide range of organisms (Table 2). Thus, ibrutinib appears to have a broad impact on the host immune system that increases likelihood of infection by a broad range of organisms, with fungi among the most visible rather than the most frequent.

In multivariate analysis advanced age, high ECOG performance score and concurrent use of steroids or other cytotoxic agents were associated with serious infection (Table 4). Notably, there was a high incidence of serious infection (50%) and IFI (15%) in patients with MCL on ibrutinib (Table 1), exceeding the rates of 28% and 2.7% respectively that were reported in a prior clinical trial of ibrutinib among MCL patients [10]. The particularly increased incidence of serious infection in MCL patients may be reflective of the presence of other risk factors. In our study, MCL patients commonly received the highest dose of ibrutinib (560 mg) (70%), prior chemotherapy (95%), concurrent steroids (15%), and tended to have elevated ECOG performance scores of $\geq$2 (30%) (Table 1). However, the potential for increased risk of serious infection in MCL patients on ibrutinib requires further investigation.

The finding of increased age and incidence of elevated ECOG performance score in patients experiencing infections while on ibrutinib is also notable. Ibrutinib was evaluated and found to be efficacious, specifically in elderly patients (>65 years) with previously untreated CLL in the RESONATE-2 trial and was considered a safer alternative to first line chemotherapy in these populations [38,39]. Ibrutinib has also been recommended as a preferred therapy for elderly patients with MCL, although a pooled analysis of multiple studies found that survival in this population was optimal in patients with ECOG of 0–1 [40,41]. Because of its perceived safety, ibrutinib may be preferentially prescribed in more elderly and frail patients.

Our study has several important limitations. Only infections requiring hospitalization within our hospital system were included, and we did not include additional follow up time after the July 1, 2019 enrollment period ending so it is possible that serious infections may have occurred after this time and were missed. However, only 30 patients in the cohort (12.3%) initiated ibrutinib less than 27 weeks (the median time to first infection) before the cut off date and therefore the number of missed infections is likely to be small. We did not evaluate for infections which did not result in hospitalization or intravenous therapy. Therefore, it is possible that significant proportion of the burden of infections treated in the outpatient setting was not captured, underestimating the impact of ibrutinib. Additionally, we included certain parameters that are known to vary considerably over time and that are difficult to accurately capture through medical record review such as neutropenia and lymphopenia.

Nonetheless, our study demonstrates that there is a high rate of serious infection in patients on ibrutinib, and these are more likely to occur in individuals who are elderly, frail, and have additional immunocompromising factors. In light of this, special consideration should be given to pre-existing risk factors for IFI and other infections in patients with hematologic malignancies who are candidates for ibrutinib. Mitigation strategies, including targeted antimicrobial prophylaxis or enhanced surveillance in those with multiple risk factors and efforts to improve functional status, may reduce the risk of infection in patients on ibrutinib.

Authorship statement

All authors meet the ICMJE criteria for authorship.

TH – Chief investigator responsible for primary data gathering, data analysis, manuscript preparation and finalization.

HC – Performed critical assistance with data gathering.

MM – Assisted with data analysis and provided critical feedback for preparation and revision of manuscript SP – Assisted with acquisition of the primary data set and provided critical insight during manuscript preparation.

II – Assisted with acquisition of the primary data set and provided critical insight during manuscript preparation.

GG – Performed statistical analyses and provided critical feedback for manuscript preparation.

YD – Performed statistical analyses and provided critical feedback for manuscript preparation.

MMA – Assisted with acquisition of data set and analysis of data derived and was heavily involved in manuscript preparation and finalization.

Declaration of competing interest

None.

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None.

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