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Incidence and characterization of fungal infections in chronic lymphocytic leukemia patients receiving ibrutinib

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Ibrutinib, a first-generation inhibitor of Bruton's tyrosine kinase (BTK), is an important therapeutic option in chronic lymphocytic leukemia (CLL) (1). In clinical trials, invasive fungal infections (IFI) were uncommon in patients taking ibrutinib, affecting 1.2% of patients (2), which was comparable to reported IFI incidence in the general CLL population (3). However, there has been subsequent reports of various fungal infections, mainly *Cryptococcus*, *Aspergillus*, and *Pneumocystis* with the use of ibrutinib. Most notably, one study reported 5 cases of *Pneumocystis jirovecii* in a 96 patient cohort of CLL patients receiving single agent ibrutinib, 4 of which were previously untreated (4). Additionally, atypical localization of fungal infections has been noted. As a result, there has been added scrutiny regarding the risk of IFI with ibrutinib (2, 5).

Recent reports have shown that ibrutinib inhibits macrophage responses, providing a potential mechanism for predisposition to certain IFI; however clinical risk factors have yet to be elucidated (6). To that end, we sought to quantify the incidence and type of IFI in CLL patients treated with ibrutinib. Secondary objectives included the description of offending fungi, IFI sites, and exploratory risk factor identification.

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We conducted a retrospective case-control study of patients ≥ 18 years of age with CLL and treated with ibrutinib (February 2014-August 2018) at The University of Texas MD Anderson Cancer Center. We included patients with ≥ 6 months of follow up data after starting ibrutinib or deceased within 6 months of starting ibrutinib. We excluded patients with prior stem cell transplantation. Patients receiving ibrutinib therapy were identified through pharmacy prescription records. IFI was defined according to revised 2019 European Organization for Research and Treatment of Cancer/Invasive fungal Infections Cooperative Group guidelines (7). In our institution, patients with CLL do not routinely receive primary antifungal prophylaxis nor do they undergo surveillance (e.g. periodic fungal biomarkers or imaging) for early diagnosis of IFI.

Only patients with proven/probable IFI diagnosed from start date of ibrutinib to 30 days after last dose of ibrutinib were included for analysis. IFIs were identified by electronic health record review. Patients in the control group had a CLL diagnosis and received treatment with ibrutinib but did not meet criteria for proven/probable IFI and had no evidence of other severe infections. Control patients were matched to IFI cases based on date of first ibrutinib dose (+/- 30 days) in a 4:1 ratio and selected for analyses based on unique institutional medical record identifier. Each control patient was only selected once. Established risk factors for infection and pertinent clinical, laboratory and radiological findings of IFI were captured for comparative analysis.

Patient demographics, CLL treatment history, causative fungal organisms, and IFI sites were collected. Potential risk factors including, diabetes, heavily pretreated CLL (≥ 3 prior lines of CLL therapy), cytotoxic chemotherapy for concomitant malignancy, and prior treatment with alemtuzumab or fludarabine were collected at any time during ibrutinib treatment for IFI cases and controls. Laboratory data including, hypoalbuminemia (< 3 g/dL), hypogammaglobulinemia (IgG < 500 mg/dL), neutropenia (< 500 cells/mm³), lymphopenia (< 1000 cells/mm³), and monocytopenia (< 80 cells/mm³) was included if within 30 days of IFI diagnosis for IFI cases, and at any time during ibrutinib treatment for controls. Glucocorticoid use (≥ 20 mg prednisone equivalents daily for ≥ 14 days) was collected if within 90 days of IFI diagnosis for IFI cases, and at any time during ibrutinib treatment for controls.

IFI incidence was determined by the proportion of proven/probable IFI divided by the total number of included patients. To determine risk factors, conditional logistic regression was used to compare patient-specific factors of IFI cases to controls. Since IFI incidence was rare, multivariable analyses were not performed. Results are reported using odds ratios with 95% confidence intervals (CI). Statistical analyses were performed using Stata software (Stata version 15.0, StataCorp LP, College Station, TX). This study was approved by the institutional review board with a waiver of informed consent.

Of the 841 patients with CLL included, we identified 21 cases of proven/probable IFI and an incidence of 2.5%. Of the 21 IFIs, the median age at diagnosis was 65 years with 81% being men. Eight (38%) patients received ibrutinib as frontline therapy, while six (29%) patients received ≥ 3 prior lines of CLL therapy. The median duration of ibrutinib treatment before IFI diagnosis was 4 months (0.5-52.2 months) (suppl table).

The most common organism identified was *Aspergillus spp.* (n=13) including six cases of *Aspergillus fumigatus* (Table 1). The remaining cases included *Cryptococcus spp.* (n=5), *Candida spp.* (n=2), *Fusarium spp.* (n=1), *Pneumocystis jiroveci* (n=1), and *Histoplasma spp.* (n=1). IFIs were mostly pneumonia (n=20); remaining cases included fungemia (n=3), skin/skin structure (n=1), CNS involvement (n=2), and sinus infections (n=1). Three patients had co-infections with multiple fungal organisms, including one patient with *Aspergillus fumigatus* and *Candida albicans*, one patient with *Aspergillus terreus* and *Cryptococcus neoformans*, and one patient with *Aspergillus spp.* and *Cryptococcus spp.* Four patients were diagnosed with disseminated IFI (Table 1). Ten patients had no classic risk factors for IFI, which included neutropenia within 30 days of infection, glucocorticoid use within 90 days of infection, or heavy pretreatment.

Importantly, 14 patients continued ibrutinib after IFI diagnosis, with six patients continuing ibrutinib for at least one year, suggesting continuation of ibrutinib after IFI diagnosis is potentially safe. Most patients continued ibrutinib at a decreased dose to account for drug interactions with antifungal agents. At date of last follow-up (6 months after IFI for each patient), 10 patients had deceased (48%). Of those patients, 5 deaths were deemed to be IFI-related (24%), 4 of which occurred within 14-days of IFI diagnosis (Figure 1).

Twenty IFI cases had data available to conduct a risk factor analysis (Table 2). Prior treatment with 3 lines of CLL therapy (OR=5.36, 95% CI 1.25-23.03) and monocytopenia (OR=6.00, 95% CI 1.41-25.45) were significantly associated with IFI in our cohort. While hypoalbuminemia (OR=17.70, 95% CI 3.84-81.46) was also associated with IFI, it was more likely a marker of active infection than a true risk factor for IFI. Other potential risk factors including, systemic glucocorticoid use, neutropenia, and hypogammaglobulinemia were not associated with increased IFI risk.

In the largest real-life cohort of CLL patients treated with ibrutinib to date, we report a 2.5% incidence of IFI, which is comparable to the incidence reported in patients with relapsed or refractory CLL treated with ibrutinib (0.5-12%) in recent retrospective studies (2, 5, 8, 9). Half of our analyzable patients (n=10) had no “classic” risk factor such as neutropenia, use of corticosteroids, or heavy pretreatment (3 lines of prior therapy). The increased incidence of severe opportunistic infections, not only IFI, in heavily pretreated CLL has been long described (10). Because of the small number of patients in observational studies and low incidence of IFI in CLL, it is difficult to determine whether ibrutinib itself led to excess IFI cases in this population. The association of IFI in heavily pretreated CLL patients on ibrutinib, was seen in some (5, 9) but not all studies (8).

A spectrum of opportunistic fungi, mainly molds, were encountered in our cohort (Table 1) and pneumonia was the predominant clinical manifestation, consistent with prior reports. Of note, a sizeable subset of our patients had polyfungal or disseminated infections, emphasizing the importance of low threshold for suspicion of widely disseminated or uncommon IFI. On the other hand, CNS involvement (3 patients with neuroimaging and 2 patients with evidence of infection) was uncommon in our patients.

Ibrutinib interacts with the immune system in several pathways and can modulate response to infections. BTK is part of a family of kinases known as Tec kinases (11). BTK and Tec are expressed on monocytes and neutrophils and play a role in control of immune functions such as chemotaxis, phagocytosis, and B-cell proliferation (11). Inhibiting BTK also prevents Toll-like receptor 9 activation of calcineurin mediated NFAT activation and reducing TNF α production (12). Relating to fungal infections, BTK inhibition has been shown to negatively affect the phagocytosis of *C. albicans* and inhibit macrophage responses to *A. fumigatus* (6, 13). It is possible that ibrutinib's immunosuppressive effects were additive to monocytopenia, a described risk factor for IFI (14).

There are multiple limitations to our study. Several clinically significant IFIs are missed due to limitations in diagnostic methods (15), combined with our study being retrospective and relied on electronic health record documentation. These factors potentially resulted in underrepresenting the true incidence of IFI. Since this was a single center study, we are unable to capture all patients diagnosed or treated at outside hospitals. Our study focused on patients with CLL and may not be applicable to patients with other lymphoid malignancies treated with ibrutinib. The small number of IFI cases limits the ability to fully assess risk factors and the magnitude of their effect.

In conclusion, our findings support active surveillance of IFI in CLL patients on ibrutinib treatment with 3 prior lines of therapy or monocytopenia. Additional studies are required to confirm risk factors for IFI and develop recommendations for appropriate antifungal prophylaxis in this patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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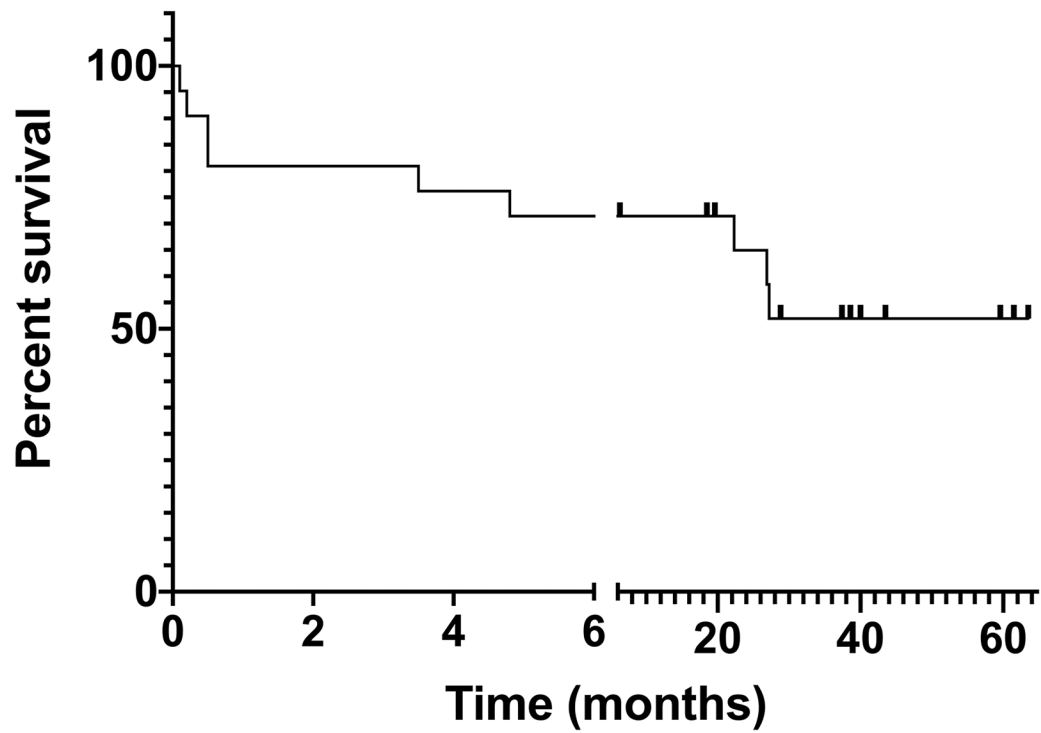


Figure 1. Overall survival of CLL patients with IFI on ibrutinib

10 of 21 patients were deceased at date of last follow-up (6 months for each patient; average 36.79 months of follow up). The first 5 deaths (4 in the first month and 1 in the fourth month) were IFI-related, while the other 5 deaths were due to disease progression or other causes.

Table 1.

Description of Invasive Fungal Infections (IFI)

IFI, n (%) ^a	
- <i>Aspergillus spp.</i>	13 (62)
- <i>Candida spp.</i>	2 (10)
- <i>Cryptococcus spp.</i>	5 (24)
- <i>Fusarium spp.</i>	1 (5)
- <i>Histoplasma spp.</i>	1 (5)
- <i>Pneumocystis jiroveci</i>	1 (5)
Site of infection, n (%)	
- Blood	3 (14)
- CNS	2 (10)
- Lung	20 (95)
- Sinus	1 (5)
- Skin/skin structure	1 (5)
- Multiple sites of infection ^b	4 (19)

^aOne patient identified through indirect testing methods (e.g. Beta-D-glucan)

^bThese include: 58-year-old male with *Candida albicans* in ascitic fluid, blood, and lungs, along with *Aspergillus fumigatus* in the ascitic fluid who deceased 13 days after IFI diagnosis; 65-year-old male with disseminated *Cryptococcus neoformans* in cerebrospinal fluid and lungs who resumed ibrutinib two months after IFI diagnosis; 59-year-old male with *Cryptococcus spp.* in his lungs and blood who resumed ibrutinib two weeks after IFI diagnosis; 65-year-old male with *Aspergillus spp.* pneumonia and a CT head concerning for CNS involvement who deceased one day after IFI diagnosis

Table 2.

Analysis of Risk Factors Comparing Patients with IFI to patients without IFI

Patient Characteristic—n (%)	Proven/Probable IFI [⊖]	No IFI N = 80	Odds Ratio (95% CI)
3 prior lines of therapy	5 (25) ^a	5 (6)	5.36 (1.25-23.03)
Prior alemtuzumab	1 (5) ^a	4 (5)	1.00 (0.11-8.95)
Prior fludarabine	8 (40) ^a	24 (30)	1.63 (0.56-4.76)
Diabetes	4 (20) ^a	11 (14)	1.50 (0.45-4.96)
Glucocorticoid use ^μ	2 (10) ^a	2 (3)	4.00 (0.56-28.40)
Prior cytotoxic chemotherapy ^τ	1 (5) ^a	2 (3)	2.00 (0.18-22.06)
Combination therapy for CLL	9 (45) ^a	38 (48)	0.97 (0.81-1.16)
Hypoalbuminemia	10 (53) ^{δ π}	4 (5) ^e	17.70 (3.84-81.46)
Neutropenia	3 (16) ^{δπ}	10 (13) ^e	1.26 (0.29-5.39)
Lymphopenia	6 (32) ^{δπ}	29 (36) ^e	0.79 (0.27-2.32)
Monocytopenia	5 (26) ^{δ π}	4 (5) ^e	6.00 (1.41-25.45)
Hypogammaglobulinemia	8 (47) ^Γ	37 (46) ^e	1.00 (0.35-2.88)

Hypoalbuminemia = albumin < 3 g/dL; Neutropenia = < 500 cells/m3; Lymphopenia = < 1000 cells/m3; Monocytopenia = < 80 cells/m3

[⊖] Patients without adequate laboratory values or follow up data within 30 days of IFI diagnosis were not included in the analysis^μ Defined as use of 20 mg/day for 14 days within 3 months prior to IFI diagnosis^τ For treatment of prior malignancy other than CLL^a N = 20^δ N = 19^Γ N = 17^π Within 30 days of IFI diagnosis^e at any time while on ibrutinib therapy