Leukemia
https://doi.org/10.1038/s41375-019-0481-1

LETTER

Chronic lymphocytic leukemia

Incidence of opportunistic infections during ibrutinib treatment for B-cell malignancies

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Received: 11 December 2018 / Revised: 12 March 2019 / Accepted: 28 March 2019

To the Editor

Ibrutinib is an oral irreversible inhibitor of Bruton's tyrosine kinase (BTK) that is FDA approved for the treatment of chronic lymphocytic leukemia (CLL), mantle cell lymphoma, Waldenstrom's macroglobulinemia, marginal zone lymphoma, and chronic graft-vs.-host disease [1–4]. An increased risk for opportunistic infection (OI) during ibrutinib treatment has been described in multiple series. Invasive fungal infections with Aspergillus species have been reported most frequently, including a 39% incidence in a study of ibrutinib for primary central nervous system lymphoma [5–7]. Additionally, a retrospective cohort study of 378 patients from Memorial Sloan Kettering reported invasive fungal infection in 4.2% of patients [8]. The risk for aspergillus has a plausible mechanism, as BTK is important in macrophage activation [9].

At the Ohio State University we follow a large and diverse cohort of patients taking ibrutinib. Therefore, we conducted a single institution retrospective cohort study to determine incidence and types of opportunistic infections in our cohort.

We reviewed records of all patients who received ibrutinib for the treatment of a hematologic malignancy between June 2010 and March 2016 using an IRB approved protocol. OI captured included *pneumocystis jirovecii* pneumonia (PJP), invasive and disseminated fungal infections, progressive multifocal leukoencephalopathy (PML), toxoplasmosis, viral disseminated infections, and atypical bacterial infections. Typical bacterial infections or localized zoster reactivation were not included. Standard search terms were used for each patient record as described in Supplemental Methods.

Baseline patient and malignancy characteristics were collected at the time of starting ibrutinib. Use of any corticosteroid equivalent to ≥20 mg prednisone for at least 4 weeks was recorded as well as the use of antimicrobial prophylaxis.

All opportunistic infections occurring during ibrutinib treatment were recorded. Infection diagnosis was determined based on treating physicians' documentation and confirmatory testing. Invasive fungal infection diagnoses were based on the revised 2008 European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) definitions [10].

Ibrutinib exposure was defined as the time from the first dose of medication until the last dose, censoring those still taking it at the last date they were seen in clinic. The person-year incidence rate for infection events was calculated using the number of infection events occurring during ibrutinib treatment divided by the total person-years of ibrutinib use. Time to OI was calculated from the date of starting ibrutinib until the onset of OI or censored at last follow-up, with discontinuation of ibrutinib, or death prior to OI as

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Supplementary information The online version of this article (https://doi.org/10.1038/s41375-019-0481-1) contains supplementary material, which is available to authorized users.

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Published online: 13 May 2019

competing events. See Supplemental Methods for additional details of the statistical analysis.

Five hundred sixty-six patients were included in the analysis. Baseline characteristics are detailed in Table 1 with laboratory values in Supplemental Table 1. The median time from diagnosis of malignancy to ibrutinib start was 6.1 years (range 0.008–33.3). The cohort consisted of mostly CLL patients (73.7%) with relapsed disease. Prior therapies are in Supplemental Table 2.

The total ibrutinib exposure for the cohort was 1225 person-years with a median exposure of 1.98 years (range 0.008–6.40) per patient. The majority of patients were treated as part of a clinical trial (80.9%). Ibrutinib was administered continuously and the dose varied according to malignancy and protocol. Ibrutinib was combined with another agent in 175 (30.9%) cases, most frequently an anti-CD20 monoclonal antibody (81.7%). The median duration of follow-up was 2.69 years (range 0.03–6.40) with CLL patients having the longest median follow-up at 2.98 years (range 0.03–6.40) and diffuse large B-cell lymphoma having the shortest at 0.30 years (0.06–4.94).

Use of antimicrobial prophylaxis was variable and the majority of patients (78.6%) received viral prophylaxis (Table 1). Less than half the patients (44.9%) received PJP prophylaxis. Sixty-five patients (11.5%) received antifungal prophylaxis, with only 16 (2.8%) receiving a drug with activity against invasive molds.

We observed 23 cases of OI in 1225 patient-years of ibrutinib exposure, resulting an incidence rate of 1.9 (95% CI: 1.2–2.8) per 100 person-years. The cumulative incidence of OI at 0.5 years was 2.3% (95% CI: 1.3–3.8%) and increased at 5 years to an estimated 4.7% (95% CI: 3.0–7.0%; Supplemental Table 3). The incidence increased the most during the first 6 months of treatment and median time from starting ibrutinib to OI development was 4.68 months (range 0.36–52.0) (Supplemental Fig. 1). Infection type, site of infection, and outcomes are listed in Table 2. No patient who received ibrutinib as first line treatment developed an OI.

The majority of OI were invasive fungal infections, which were observed in 17 (73.9%) OI patients, and invasive aspergillosis was the most frequent type ($n = 12$, 52.1%). Invasive fungal infections occurred at a median of 4.0 months (range 0.3–52.0) after starting ibrutinib. Importantly, none of these patients were on mold active prophylaxis at the time of OI diagnosis. The incidence of OI other than invasive fungal infections at 0.5 years was 0.4% (95% CI: 0.1–1.2%) and increased to 1.2% (95% CI: 0.5–2.5%) by 5 years. Characteristics of all patients with OI, laboratory values at OI diagnosis, treatment modality, and outcomes are summarized in Supplemental Tables 4–6.

Among the 23 patients with OI, the median survival from time of OI diagnosis was 1.39 years (95% CI: 0.38-NR).

Table 1 Baseline characteristics of the cohort

Characteristics	No. = 566	
Age, median (range)	65 (23–98)	
Men, no. (%)	397 (70.1)	
ECOG performance status of 0 or 1, no. (%)	515[a] (92.5)	
Prior treatments, median (range)	3 (0–18)	
Malignancy type	No.	%
Chronic lymphocytic leukemia	417	73.7
Mantle cell lymphoma	56	9.9
Diffuse large B-cell lymphoma[b]	35	6.2
Follicular lymphoma	15	2.7
Hairy cell leukemia	13	2.3
Richter's Syndrome[c]	12	2.1
Waldenstrom's macroglobulinemia	11	1.9
Marginal zone lymphoma	6	1.1
Prolymphocytic leukemia	1	0.2
Medical comorbidities	No.	%
Hypertension	248	43.8
Diabetes	71	12.5
Chronic kidney disease	68	12.0
Pulmonary disease	52	9.2
Autoimmune disease	22	3.9
Liver disease	15	2.7
Human immunodeficiency virus (HIV) infection	1	0.2
Solid organ transplant	1	0.2
Antimicrobial prophylaxis	No.	%
Viral	445	78.6
Valacyclovir	290	51.2
Acyclovir	150	26.5
Famciclovir	3	0.5
Valganciclovir	2	0.4
None	121	21.4
Pneumocystis jirovecii pneumonia	254	44.9
Bactrim	221	39.0
Dapsone	26	4.6
Atovaquone	5	0.9
Pentamidine	2	0.4
None	312	55.1
Fungal	65	11.5
Fluconazole	46	8.1
Voriconazole	13	2.3
Posaconazole	3	0.5
Caspofungin	3	0.5
None	501	88.5

ECOG Eastern Cooperative Oncology Group

[a]Out of 557 with available data

[b]Including transformed lymphomas

[c]Any lymphoma in a patient with chronic lymphocytic leukemia

Table 2 Opportunistic infections observed during ibrutinib treatment

Type of infection	No. (%) total = 23	Location(s)	Alive[a]
Fungal	17 (74)		
Aspergillosis[b]	12	Lung (10), brain (1), Lung/hepatic (1)	Y (5), N (7)
Mucormycosis[c]	2	Sinuses (1), brain (1)	Y (2)
Cryptococcosis	1	Disseminated (1)	Y (1)
Blastomycosis	1	Disseminated (1)	N (1)
Histoplasmosis	1	Disseminated (1)	Y (1)
Bacterial	2 (7)		
MAC	2	Lung (2)	Y (1), N (1)
Viral	3 (13)		
JC virus (PML)	2	Brain (2)	N (2)
BK virus	1	Urinary (1)	Y (1)
Parasite	1 (4)		
Toxoplasmosis	1	Chorioretinitis (1)	Y (1)

MAC mycobacterium avium complex, *PML* progressive multifocal leukoencephalopathy

[a]At last follow-up

[b]Probable pulmonary aspergillosis ($n = 9$), proven aspergillosis ($n = 3$)

[c]Both proven mucomycosis

Those who died after OI diagnosis had a median survival of 0.14 years (range 0.02–4.47).

In univariable models, ≥3 prior treatments (HR 2.61), diabetes mellitus (HR 3.03), pulmonary disease (HR 2.81), chronic kidney disease (HR 2.56), and liver disease (HR 6.42) were associated with an increased risk for OI ($p < 0.05$). In multivariable analyses, ≥3 prior treatments (HR 2.87, 95% CI: 1.12–7.35; $p = 0.028$), diabetes (HR 3.63, 95% CI: 1.50–8.77; $p = 0.004$), and liver disease (HR 7.53, 95% CI: 2.14–26.49; $p = 0.002$) were independently associated with OI development (Supplemental Table 7).

Consistent with prior reports, our study confirms that invasive fungal infections are observed with ibrutinib therapy. While the incidence of these was relatively low (1.4 per 100 person-years), it is higher than we would anticipate from the underlying malignancy alone. We found cases of other OI, including MAC, PML, and Toxoplasmosis, however, incidence was very low (0.4% of the cohort). The occurrence of PML was not unanticipated as majority of patients were exposed to anti-CD20 monoclonal antibodies [11].

It is notable that we did not identify a single case of PJP. Previous data estimated an incidence of 2.05 cases per 100 patient-years and would predict 25 cases in our cohort [7]. As 55.1% of our cohort did not receive prophylaxis against PJP we would have expected to see multiple cases. Therefore, our data does not support the routine use of PJP prophylaxis in patients receiving ibrutinib.

Similar to a recent study, we identified ≥3 prior treatments as a risk factor for OI development, which is unsurprising as prior treatment is associated with worsening immune function and heightened infection risk in other settings [8]. Liver disease and diabetes were associated with increased risk of infection, which may be because they impair inflammatory response along with neutrophilic and phagocytic dysfunction [12–14]. It is important to note that liver disease in our study was based on history of a liver condition and not on liver function tests during ibrutinib treatment.

If these factors associated with risk for OI are confirmed in other cohorts, this may have implications for patient selection for ibrutinib or for prophylactic antimicrobial therapy. Surprisingly, we found conventional infection risk factors, including age and baseline cytopenias, not to be associated with OI in this cohort. Use of antimicrobial prophylaxis was not associated with decreased OI risk likely due to only 2.8% of patients received mold active prophylaxis. More data is needed to examine whether antifungal prophylaxis is appropriate for high-risk patients, especially considering the significant drug interactions from strong or moderate CYP3A inhibition [15].

There are several important limitations of our study. As a retrospective study where 19.1% of patients were not enrolled in a prospective clinical trial, episodes of OI were not rigorously assessed and treated using a uniform method, which could lead to missed events. The study is single-site, so events occurring at other hospitals may not have been captured, although the last follow-up always occurred at our site. Furthermore, the study was largely (80.9%) on clinical trial participants, which is different from patients seen in general practice so findings may not apply to a non-trial population. The site location in Ohio may limit the generalizability of our results as exposures to organisms that cause OI may be different in other locations. Also, use of antimicrobial prophylaxis was variable and not uniform across the cohort. Lastly, our cohort included few patients who received ibrutinib as a first therapy, so further evaluation of infectious risk in this setting is required.

In conclusion, we found that invasive fungal infections occur at a low frequency during ibrutinib therapy, with aspergillus being the most common infectious organism. Further work is needed to confirm risk factors and determine the optimal monitoring and prophylaxis for these patients.

Acknowledgements We would like to thank the Ohio State University Division of Hematology for support of this project. We would also like to acknowledge our colleagues who provided the clinical care for the included patients. Research reported in this publication was supported in part by the Ohio State University Comprehensive Cancer Center and the National Institutes of Health under grant number P30 CA016058. This work was also supported in part by K23 CA178183, R01 CA197870, and R35 CA197734.

Compliance with ethical standards

Conflict of interest The authors have the following disclosures: KAR received research funding from Genentech and consults for Acerta Pharma. SAB is on a speakers' bureau for Janssen and Pharmacyclics. JCB receives research funding from Genentech, Acerta Pharma, Pharmacyclics, and Janssen. JAW received honoraria from Janssen, has consulted for Janssen, and receives research funding from MorphoSys, Karyopharm Therapeutics, and AbbVie. FTA has consulted for AbbVie, Gilead Sciences, AstraZeneca, Sunesis, Genentech, and Janssen, served on the speakers' bureau for Abbvie and AstraZeneca, and received research funding from Pharmacyclics. LM, QZ, TEW, ZEB, TG, LBL, FL, PS, AS, and MS declare that they have no conflict of interest.

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