Low risk of *Pneumocystis jirovecii* pneumonia and invasive aspergillosis in patients with Waldenström macroglobulinaemia on ibrutinib

Waldenström macroglobulinaemia (WM) is a B cell lymphoma that is commonly associated with the the activation of nuclear factor-κB via Bruton tyrosine kinase (BTK) (Yang *et al*, 2013). Ibrutinib, a BTK inhibitor, is US Food and Drug Administration-approved for the treatment of chronic lymphocytic leukaemia (CLL), mantle cell lymphoma, marginal zone lymphoma and WM (https://www.imbruvica.com/docs/librariesprovider7/default-document-library/prescribing-information.pdf).

Patients with CLL and other lymphoid malignancies receiving ibrutinib therapy are at risk for developing invasive fungal disease (IFD), including *Pneumocystis jirovecii* pneumonia (PCP) and invasive aspergillosis (IA) (Arbona-Haddad *et al*, 2018; Varughese *et al*, 2018). Most patients who develop these infections while on ibrutinib do not exhibit classical risk factors for IFD, such as neutropenia, lymphopenia or corticosteroid treatment (Varughese *et al*, 2018).

Fungal infections in patients with CLL and other lymphoid malignancies receiving ibrutinib may be due to the off-target effect of the drug on the adaptive immune system (Lionakis *et al*, 2017). Whether this increased risk of infection is caused by ibrutinib alone or in combination with immune dysregulation from the underlying malignancy is unknown. The objective of this study was to assess the risk of PCP and IA in WM patients receiving ibrutinib, in order to guide decisions regarding antimicrobial prophylaxis.

A retrospective study was performed of all adult patients with WM who initiated ibrutinib at Dana-Farber Cancer Institute (DFCI) between 28 May 2012 and 30 January 2018. Patients were followed until 1 April 2018 for the development of PCP and IA. The study was approved by the Dana-Farber/Harvard Cancer Center Office for Human Research Studies.

Covariates of interest included patient age, sex, previous treatment regimens, antimicrobial medications, and length of exposure to ibrutinib. In- and out-patient medical records were reviewed for cases of PCP and IA. These records were reviewed for exposure to prophylactic or treatment agents to these pathogens, including atovaquone, trimethoprim-sulfamethazole, voriconazole, posaconazole, and isavuconazole.

Invasive fungal disease was assessed by two infectious diseases specialists and was classified per the European Organization for Research and Treatment of Cancer (EORTC)/Invasive Fungal Infections and Mycoses Study Group (IFI and MSG) (De Pauw *et al*, 2008). Patients who participated in clinical trials at DFCI had adverse events-reporting logs verified to ensure completeness of data collection. We calculated exact 95% confidence limits for the binomial proportion (Clopper & Pearson, 1934) using SAS® 9·4 (SAS Institute, Cary, NC, USA).

In total, 217 WM patients were treated with ibrutinib during the study period. Their baseline and clinical characteristics are presented in Table I. One hundred and forty (65%) were male, and the median age at initiation of ibrutinib was 67 years (range, 43–93). Ibrutinib was initially prescribed at a dose of 420 mg/day in all patients and was administered in a continuous fashion. Fifty-eight patients (27%) had a dose reduction due to adverse events or interactions with concomitant medications; 46 (21%) to 280 mg/day and 12 (6%) to 140 mg/day. No patient received concomitant immunosuppressive therapy; 153 patients (71%) had been treated with different chemotherapeutic regimens prior to starting ibrutinib, with a median of two (range, one to eight) previous treatment regimens (Table I).

The median duration of ibrutinib exposure was 23·4 months (range 0·3–71·1 months) and there were a total of 506 observed person-years of ibrutinib exposure. Two hundred and six patients (95%) received ibrutinib continuously for at least 3 months and 163 (75%) received it continuously for at least 1 year. Seventeen patients (8%) received prophylactic trimethoprim-sulfamethoxazole (n = 14) or atovaquone (n = 3) during the study period. There were no incident cases of PCP. Utilizing observations from 148 individuals not receiving prophylaxis, the estimated risk of PCP with 1 year of ibrutinib for WM was 0% (95% CI 0–2·46%).

No patients received prophylactic anti-fungal therapy. One patient developed probable IA per the EORTC/IFI and MSG diagnostic criteria after recently discontinuing ibrutinib due to pancytopenia. The patient was then started on bendamustine and rituximab and was subsequently diagnosed with IA 5 weeks later; the patient had not received steroids or nucleoside analogues. While antifungal therapy was initiated promptly, the patient died 2 weeks later due to underlying disease progression. Twenty-two other patients died during the study period; none had evidence of IFD. The 1 year risk of IA while receiving ibutinib for WM was 0·6% (95% CI 0·02–3·35%).

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Table I. Patient characteristics.

Characteristic	
Age at ibrutinib initiation, years; median (range)	67 (43–93)
Male sex	140 (65%)
Participated in a clincal trial	73 (34%)
Presence of *MYD88* mutation*	190 (98%)
Time from diagnosis to start of ibrutinib, years; median (range)	3·4 (0–25·2)
Length of ibrutinib exposure, days; median (range)	703 (8–2134)
Indications for treatment	
Anaemia	120 (55%)
Constitutional symptoms	70 (32%)
Hyperviscosity	36 (17%)
Thrombocytopenia	14 (6%)
Extramedullary disease	26 (12%)
Neuropathy	17 (8%)
Response to treatment†	
Very good partial response	53 (24%)
Partial response	111 (51%)
Minor response	37 (17%)
No response	16 (7%)
Previous treatment regimens, n; median (range)	2 (1–8)
Anti-CD20 monoclonal antibody‡	142 (65%)
Proteasome inhibitor§	80 (37%)
Alkylating agent¶	81 (37%)
Nucleoside analogue**	34 (16%)
Prophylactic antimicrobial medications	
Trimethoprim-sulfamethoxazole	14 (6%)
Atovaquone	3 (1%)
Voriconazole	0
Posaconazole	0
Isavuconazole	0
Infections	
Invasive aspergillosis	1 (0·5%)
Pneumocysitis jirovecii pneumonia	0

All values are reported as n (%) unless otherwise stated.

*Among 194 genotyped patients.

†Treatment responses were assessed using the current consensus criteria adopted at the 6th International Workshop for Waldenstrom's Macroglobulinaemia (Owen *et al*, 2013).

‡Monoclonal antibodies included rituximab and ofatumumab.

§Proteasome inhibitors included bortezomib and carfilzomib.

¶Alkylating agents included cyclophosphamide and bendamustine.

**Nucleoside analogues included fludarabine and cladribine.

Although ibrutinib has been associated with developing IFD, most of the reported data involved patients who were treated with ibrutinib for CLL (Arbona-Haddad *et al*, 2018; Varughese *et al*, 2018). For example, DFCI data suggest that the occurrence of IFD is 12·8% among patients with CLL or non-Hodgkin lymphoma treated with BTK or phosphatidylinositol-3-kinase (PI3K) inhibitors (Arbona-Haddad *et al*, 2018). The increased risk of IFD in patients with CLL and other lymphoid malignancies receiving ibrutinib therapy appears to be multi-factorial, including additive effects from previous immunosuppressive therapies, direct effects on BTK signalling in immune cells, as well as off-target effects on other kinases (Chamilos *et al*, 2018). In addition to these factors, our data also suggest a role for additional immunosuppression associated with the patient's underlying malignancy, as WM patients on ibrutinib appear to have a lower risk of PCP and IA than patients with CLL on BTK inhibitors.

Our study is limited by the relatively small sample size used to evaluate infectious outcomes. However, it is the largest cohort of WM patients that assessed the risk of these infectious complications on ibrutinib. We also included a diverse patient population, encompassing those who previously received several treatment regimens prior to initiating ibrutinib, which should increase the generalizability of our results. As data collection was obtained from medical record review, this study could not exclude mild or sub-clinical cases IFD in patients who did not seek medical attention for these events.

In conclusion, this study suggests a differential incidence of IFD among different patient populations receiving ibrutinib therapy. As prophylaxis against PCP in haematological patients is typically recommended at incidence rates ≥5% (Rodriguez & Fishman, 2004), our results suggest that antimicrobial prophylaxis does not appear to be warranted in WM patients receiving ibrutinib in the absence of additional risk factors. Further research into the mechanisms of increased susceptibility to PCP and IA in patients receiving ibrutinib therapy for other lymphoid malignancies is warranted.

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Author contributions

The study was conceptualized by NCI and MPC. Medical record review was performed by AEK and MPC. The manuscript was written by AEK and MPC with critical input from all co-authors. Statistical analysis was performed by MPC and SLDP. All authors have reviewed the manuscript and agree to its submission in its current form.

Disclosures and conflicts of interest

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