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Infections in patients with lymphoproliferative diseases treated with targeted agents: SEIFEM multicentric retrospective study

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Summary

We describe the opportunistic infections occurring in 362 patients with lymphoproliferative disorders treated with ibrutinib and idelalisib in clinical practice. Overall, 108 of 362 patients (29·8%) developed infections, for a total of 152 events. Clinically defined infections (CDI) were 49·3% (75/152) and microbiologically defined infections (MDI) were 50·7% (77/152). Among 250 patients treated with ibrutinib, 28·8% (72/250) experienced one or more infections, for a total of 104 episodes. MDI were 49% (51/104). Bacterial infections were 66·7% (34/51), viral 19·6% (10/51) and invasive fungal diseases (IFD) 13·7% (7/51). Among the 112 patients treated with idelalisib, 32·1% (36/112) experienced one or more infections, for a total of 48 episodes. MDI were 54·2% (26/48). Bacterial infections were 34·6% (9/26), viral 61·5% (16/26) and IFD 3·8% (1/26). With ibrutinib, the rate of bacterial infections was significantly higher compared to idelalisib (66·7% vs. 34·6%; $P = 0·007$), while viral infections were most frequent in idelalisib (61·5% vs. 19·6%; $P < 0·001$). Although a higher rate of IFD was observed in patients treated with ibrutinib, the difference was not statistically significant (13·7% vs. 3·8% respectively; $P = 0·18$). Bacteria are the most frequent infections with ibrutinib, while viruses are most frequently involved with idelalisib.

Keywords: infections, lymphoproliferative diseases, targeted therapy.

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Introduction

In the past decade, a multitude of new agents have become available for treatment of lymphoproliferative disorders. So called "molecular targeted drugs" are now used in clinical practice, such as ibrutinib and idelalisib, together with a number of monoclonal antibodies. Efficacy and safety of these agents were mainly assessed in registration trials and most data about infections are derived from those studies or retrospective analyses at referral centres, not necessarily representative of the overall population.

Infections occur at least once in more than 50% of chronic lymphocytic leukemia (CLL) patients, contributing to 30%–50% of deaths.[1-3] In patients with CLL, the reported risk of infection following treatment with ibrutinib alone or in combination with other agents ranges from 4% to 29%.[4-9] In a recent retrospective single institution study of 566 patients, the reported rate of opportunistic infections is 4%, although typical bacterial infections or localised zoster reactivations were not included.[4]

Significantly high risk of infection is reported in clinical trials with the use of ibrutinib for patients with refractory/relapsed disease.[10-13] Although partial reconstitution of humoral immune system has been reported,[10] the molecule itself is reported to potentially affect cell-mediated immunity.[14]

In clinical trials with ibrutinib, fungal infections are occasionally reported;[8] nevertheless, with extensive use, there have been a number of reports of invasive aspergillosis (IA), pneumocystis jirovecii pneumonia (PJP) and lomentospora (scedosporium) prolificans.[15-17] After adjustment for duration of drug exposure, ibrutinib as monotherapy, or in combination with chemo-immunotherapies, may not be associated with additional risk for infection.[6,18] However, a recently published meta-analysis of seven randomised clinical trials with ibrutinib[19] showed significant increased incidence rate of infections.

Long-lasting therapy with idelalisib may be associated with an overall increased risk of infections.[9] Increased risk of opportunistic infections continued to be observed in studies of idelalisib in combination with bendamustine and rituximab, and rates of cytomegalovirus (CMV) reactivations were reported up to five times higher in patients managed with idelalisib compared to control arms.[20-22]

We conducted a retrospective evaluation of incidence and characteristics of opportunistic infections in a large and diverse cohort of patients treated with ibrutinib and idelalisib, single agents or in combination as licensed, in a large number of haematology centres across Italy.

Methods

This retrospective observational study was conducted in Italy in 14 haematological tertiary care centres or university hospitals participating to the Sorveglianza Epidemiologica Infezioni nelle Emopatie (SEIFEM) group.

The analysis was based on clinical records of adults (aged over 18) affected by haematological malignancies treated with ibrutinib and idelalisib, single agents or in combination. Patients were treated from time of commercial availability of the two drugs in Italy (idelalisib from March 2015 and ibrutinib from January 2016) until December 2016. The observation period was one year after study entry and the study was terminated in April 2018.

Patients enrolled in clinical trials or treated within patient named programs were excluded, as well as patients with active infections at beginning of treatment. Each participating centre provided the total number of patients treated and clinical and laboratory details about patients who experienced infections. Sensible data pseudonymisation was applied to comply with the European Union's new general data protection regulation.

The diagnostic work-up at onset of fever did not significantly differ among centres and included the use of microbiological data, CT scans, X-rays, bronchoalveolar lavage and histological examination.

Infections were defined according to criteria reported by the Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN).[23]

For each infective episode, the following information were collected: patient demographics, therapy line, comorbidities, presence of central venous catheter (CVC), neutropenia (<500 cells/mm^3), lymphopenia (<200 cells/mm3), concurrent or prior steroid therapy (prednisone/prednisolone for at

least 10 days at a dosage of 25 mg minimum or equivalent dosage), anti-infection prophylaxis and prior haemopoietic stem cell transplant procedure.

Clinically documented infection (CDI) was defined as presence of clinical or radiographic features of infection such as cellulitis or pneumonia, without microbiologic confirmation. Microbiologically documented infection (MDI) was defined as positive cultures from any significant site.[24]

Severity of infections was graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 5·0, 2017.

Invasive fungal Disease (IFD) was defined according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group (MSG).[25]

For each infective episode, suspension or discontinuation of the targeted drug as well as the outcome of the infection was evaluated.

Multiple infections occurring in the same patient were considered separately, unless caused by the same agent.

Mortality rate was defined as the number of deaths in the referenced population. We defined cause-specific mortality due to infection when patients died with clinical evidence and/or microbiological signs of infection. Lethality rate was defined as the number of deaths over number of patients with infection.

The ethical committee of each participating site approved the protocol. The committee stated that this retrospective study was in compliance with the 1964 Helsinki Declaration and its later amendments, and the requirement for informed patient consent was waived.

Statistical analysis

Continuous variables were compared by Student's *t*-test for normally distributed variables and the Mann-Whitney U-test for non-normally distributed variables. Categorical variables were evaluated using the χ^2 or two-tailed Fisher's exact test as appropriate. Values are expressed as means ± standard deviation (SD) (continuous variables), or as percentages of the group from which they were derived (categorical variables). Two-tailed tests were used to determine statistical significance; a *P*-value of <0·05 was considered significant. The Kaplan-Meier method was used for time-to-infection analysis. Regression analysis for dependent variables was evaluated with probit model and Cochran–Mantel–Haenszel test (CMH). All statistical analyses were performed using Stata, version 16 (Stata Corporation, College Station, Texas, USA).

Results

A total number of 362 patients were treated with one of the two agents as monotherapy or in combination with other agents. The overall rate of patients with infections was 29·8% (108/362).

Table I. Characteristics of 108 patients with infections.

	Ibrutinib *N* = 72	Idelalisib *N* = 36
Age, median (range)	68·6 (50–86)	68·5 (49–84)
Sex, male N (%)	49 (68·1)	27 (75)
Medical comorbidities, N (%)		
• Diabetes	11 (15·3)	8 (22·2)
• COPD	7 (9·9)	5 (13·9)
• Renal failure	6 (8·3)	6 (16·7)
Prior treatments, N (%)		
• < 3	43 (59·7)	17 (47·2)
• ≥ 3	29 (40·3)	19 (52·8)
Hematological malignancies, N (%)		
• CLL		
Upfront	4 (5·6)	1 (2·8)
R/R	58 (80·6)	28 (77·8)
• NHL FL R/R	0	7 (19·4)
• MCL R/R	6 (8·3)	0
• LPL R/R	4 (5·6)	0
Therapy		
• monotherapy	70 (97·2)	12 (33·3)
• combination	2 (2·8)	24 (66·7)
Infective events N	104	48
• Grade < 3	57 (54·8)	24 (50)
• Grade ≥ 3	47 (45·2)	24 (50)
Infective events N	104	48
• CDI	53 (51)	22 (45·8)
• MDI	51 (49)	26 (54·2)
Antimicrobial prophylaxis, N (%)		
• Antiviral	34 (47·2)	28 (77·8)
• Antifungal	1 (1·4)	1 (2·8)
• AntiPJP	54 (75)	34 (94·4)
Risk factors		
• Neutropenia	11 (15·3)	9 (25)
• Lymphopenia	4 (5·6)	4 (11·1)
• CVC	4 (5·6)	5 (13·9)
• Transplant	1 (1·4)	4 (11·1)
• MDR colonisation	3 (4·2)	0
• Steroid treatment	24 (33·3)	12 (33·3)
• Prior		

Table I. (*Continued*)

	Ibrutinib $N = 72$	Idelalisib $N = 36$
Concomitant	14 (19·4)	7 (19·4)
Days from treatment start to first infection, median (range)	148·7 (3–830)	175·3 (9–690)

The rate of patients with two or more infective episodes was 26·9% (29/108). Characteristics of the 108 patients are reported in Table I.

Of 152 infective episodes, 46·7% (71/152) were classified of grade ≥3, with an overall infection mortality rate of 4·1% (15/362) and infection lethality rate of 13·9% (15/108).

MDI accounted for 50·7% (77/152), while CDI were 49·3% (75/152).

Ibrutinib

Characteristics of patients are reported in Table I. Two-hundred-fifty patients were treated with ibrutinib, and 28·8% (72 of 250) experienced at least one infection, for a total of 104 episodes. The rate of patients that experienced two or more infective episodes was 29·2% (21/72).

Involved sites of infections are reported in Table II.

In 48·1% of episodes (50/104), the resolution of the infective event was obtained without ibrutinib suspension or discontinuation, while in 37·5% of cases (39/104) ibrutinib was suspended and in 14·4% (15/104) was discontinued.

MDI accounted for 49% of episodes (51/104). The different etiology of infections is reported in Table III. The overall rate of bacterial infections was 9·6% (24/250). Bacterial infections were due to Gram negatives in 67·6% of cases (23/34), while Gram positives accounted for 17·6% of cases (6/34) and polymicrobial were 14·7% (5/34). Bloodstream infections (BSI) due to bacteria were caused in two cases by Gram negatives (*Bacteroides thetaiotamicron, E. coli*), in two by Gram positives (*E. faecium, C. ramosum*) and one polymicrobial (*E.coli* + *S. gallolyticus*).

Table II. Sites of infections.

	Ibrutinib (%)		Idelalisib (%)	
	MDI *N* 51 (49)	CDI *N* 53 (51)	MDI *N* 26 (54)	CDI *N* 22 (46)
LRTI	18 (35·3)	26 (49)	6 (23·1)	12 (54·4)
BSI	6 (11·8)	0	2 (7·7)	0
GITI	4 (7·8)	0	2 (7·7)	1 (4·5)
SSTI	3 (5·9)	9 (17)	1 (3·8)	2 (9·1)
UTI	14 (27·4)	3 (5·7)	3 (11·5)	0
CNS	2 (3·9)	0	1 (3·8)	0
FUO	0	4 (7·5)	0	6 (27·3)
URTI	1 (2)	11 (20·8)	2 (7·7)	1 (4·5)
CMV/EBV reactivation	3 (5·9)	0	9 (34·6)	0

Table III. Etiology of MDI.

	Ibrutinib *N* (%)	Idelalisib *N* (%)	*P*-value
Bacterial	34 (66·7)	9 (34·6)	**0·007**
Viral	10 (19·6)	16 (61·5)	**< 0·001**
Fungal	7 (13·7)	1 (3·8)	0·25
Total	51 (100)	26 (100)	

Bold values indicate statistical significance (*P*-value < 0·05).

Ibrutinib was suspended in 32·3% of cases of bacterial infection (11/34) and discontinued in 8·8% of cases (3/34).

The overall rate of IFD was 2·8% (7/250). Seven cases of proven IFD were reported in seven patients, accounting for 6·7% of 104 infective episodes. There were five cases of invasive pulmonary aspergillosis (IPA), one case of candidemia (*C. albicans*) and one case of invasive aspergillosis (IA) of CNS confirmed at autopsy. Treatment with ibrutinib was suspended in 28·6% of cases of IFD (2/7) and resumed at infection resolution, while it was discontinued in 71·4% (5/7).

The overall rate of viral infections was 3·6% (9/250). Ten episodes of viral infections were reported and 40% (4/10) were graded ≥3. Two were cases of viral pneumonia-caused CMV and influenza A H1N1. Three cases were viral reactivations (CMV, EBV and HBV, respectively). There was one single case of upper respiratory tract infection (URTI) by Cocksakie virus. Two cases of skin/soft tissue infection (SSTI) due to HSV1 and HHV6 were reported. Two cases of urinary tract infection (UTI) by BK virus also occurred.

In 50% of cases (5/10), therapy with ibrutinib was suspended and resumed at the resolution of the infection, while ibrutinib was discontinued in 10% (1/10) cases of viral infection.

Median time from treatment start and the onset of the first infection was 148·2 days (range 3-830) (Fig 1A).

The majority of infectious events, 49% (51/104), occurred within 90 days of treatment, while 15·4% (16/104) occurred between 90 and 180 days and 35·6% (37/104) after 180 days (Fig 2A). During the first 90 days of treatment, CDI were reported in 23·1% episodes (24/104), bacterial infections accounted for 17·3% episodes (18/104), viral infections for 4·8% (5/104) and IFD for 3·8% (4/104). Between 90 and 180 days of treatment, CDI were reported in 8·7% events (9/104), bacterial infections in 3·8% cases (4/104), viral infections in 1·9% (2/104) and IFD in 1% (1/104). Beyond 180 days of treatment, CDI were reported in 19·2% events (20/104), bacterial infections accounted for 11·5% (12/104) and viral infections for 2·9% (3/104) and 1·9% (2/104) were IFD (Fig 2A).

The overall infection mortality rate in patients treated with ibrutinib was 2·8% (7/250). Four patients died of IFD (two IPA, one IA of CNS and one BSI by *C. albicans*). One patient died of complicated UTI by *E. coli* and two for LRTI not microbiologically documented.

Univariate analysis of several risk factors (i.e., age, sex, diabetes, COPD, renal failure, haematological malignancy, prior treatment, neutropenia, lymphopenia, MDR colonisation, CVC, transplant, steroid treatment, bacterial/viral/fungal etiology) showed that the only variable significantly associated with infection mortality was the fungal etiology (P = 0·001).

Idelalisib

Characteristics of patients are reported in Table I. There were 112 patients treated with idelalisib, and 32·1% (36/112) experienced one or more infections, for a total of 48 episodes. In 22·2% of patients (8/36), two or more infective episodes occurred. Sites of infections are reported in Table II

The overall rate of bacterial infections was 8% (9 of 112 patients). Among MDI bacterial infections were reported in 34·6% of cases (9/26), viral infections/ reactivations in 61·5% (16/26) and IFD in 3·8% (1/26) (Table III).

There were 9 bacterial infections, caused by Gram negatives in 77·8% of cases (7/9) and Gram positive in 11·1% of cases (1/9). Two BSI were caused by *E. coli* ESBL and by *Enterococcus fecalis*, respectively. Three cases of pneumonia were caused respectively by *Bordetella bronchiseptica, Pseudomonas aeruginosa* and *Haemophylus parainfluenzae*. Two cases of gastrointestinal tract infection (GITI) were due to *Salmonella* and *Campylobacter*. Two cases of bacterial UTI were reported, one by *E. coli* and one polymicrobial (*K. pneumoniae* and *Enterococcus fecalis*).

The overall rate of viral infections/reactivations at patient level was 9·8% (11/112 patients).

Among 26 reported MDI, viral infections/reactivations accounted for 16 events (Table III). Viral reactivations (six CMV and three EBV) constituted 56·3% of them (9/16). Other viral infections included two cases of LRTI caused by Influenza virus A, two cases of URT infection by H1N1, one case of SSTI by HSV1, one case of BK virus UTI and one case of JCV CNS infection.

The overall rate of IFD was 0·9% (1/112) and was represented by a single case of PJP that occurred in one patient not receiving anti-PJP prophylaxis.

The median time from start of idelalisib and the first infective episode was 175 days (range 9–690) (Fig 1B).

The majority of infectious complications occurred after 180 days of treatment (45·8%; 22/48), 29·2% (14/48) within 90 days and 25% (12/48) between 90 and 180 days (Fig 2B) During the first 90 days of treatment CDI were diagnosed in 14·6% of episodes (7/48), bacterial infections accounted for 2·1% (1/48), viral infections for 10·4% (5/48) and IFD for 2·1% (1/48). Between 90 and 180 days of treatment, CDI were reported in 4·2% events (2/48), bacterial infections accounted for 6·3% (3/48), viral infections for 14·6% (7/48). Beyond 180 days, CDI were reported in 27·1% events (13/48), bacterial infections accounted for 10·4% (5/48) and viral infections for 8·3% (4/48). No fungal infections were reported beyond 90 days of treatment.

In 29·2% of episodes (14/48), the infection resolved without idelalisib suspension or discontinuation. In 54·2% of cases (26/48), treatment was suspended, and in 16·7% (8/48) it was discontinued.

Eight patients died of infection, with an overall infection mortality rate of 7·1% (8/112). Microbiologically documented causes of death were one PJP, one JCV encephalitis and one pneumonia by Influenza virus A. Four other patients died of clinically documented pneumonia and one of septic shock without microbiological evidence. None of the risk factors included in the univariate analysis (age, sex, diabetes, COPD, renal failure, haematological malignancy, prior treatment, neutropenia, lymphopenia, MDR colonisation, CVC, transplant, steroid treatment, bacterial/viral/fungal etiology) were significantly correlated with infection mortality.

The overall infection mortality rate did not differ significantly between patients treated with ibrutinib (7/250) and those who received idelalisib (8/112) (2·8% vs. 7·1%, respectively; P = 0·055).

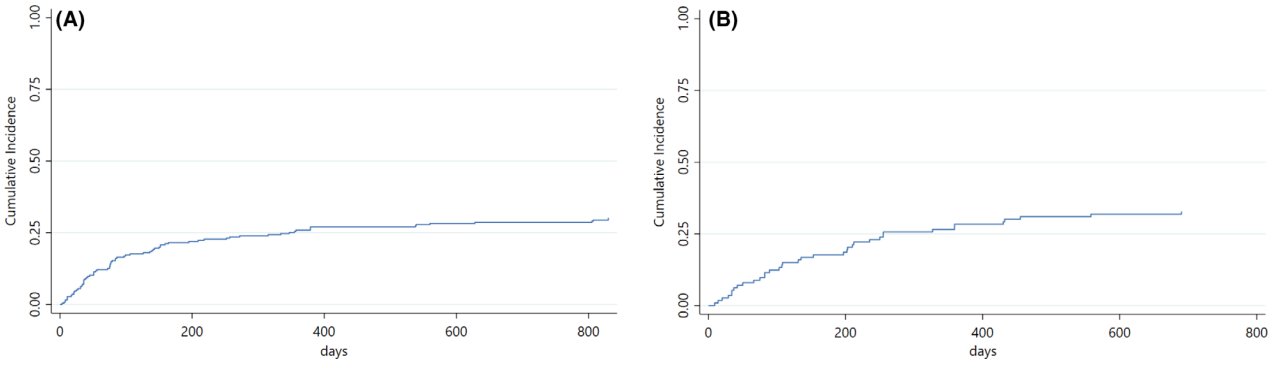

Fig 1. Cumulative incidence of infections. (A) 250 patients treated with ibrutinib of which 72 experienced infections (104 events). Median time to first infection: 148·2 days (range 3–830); (B) 112 patients treated with idelalisib of which 36 experienced infections (48 events). Median time to first infection: 175 days (range 9–690). [Colour figure can be viewed at wileyonlinelibrary.com]

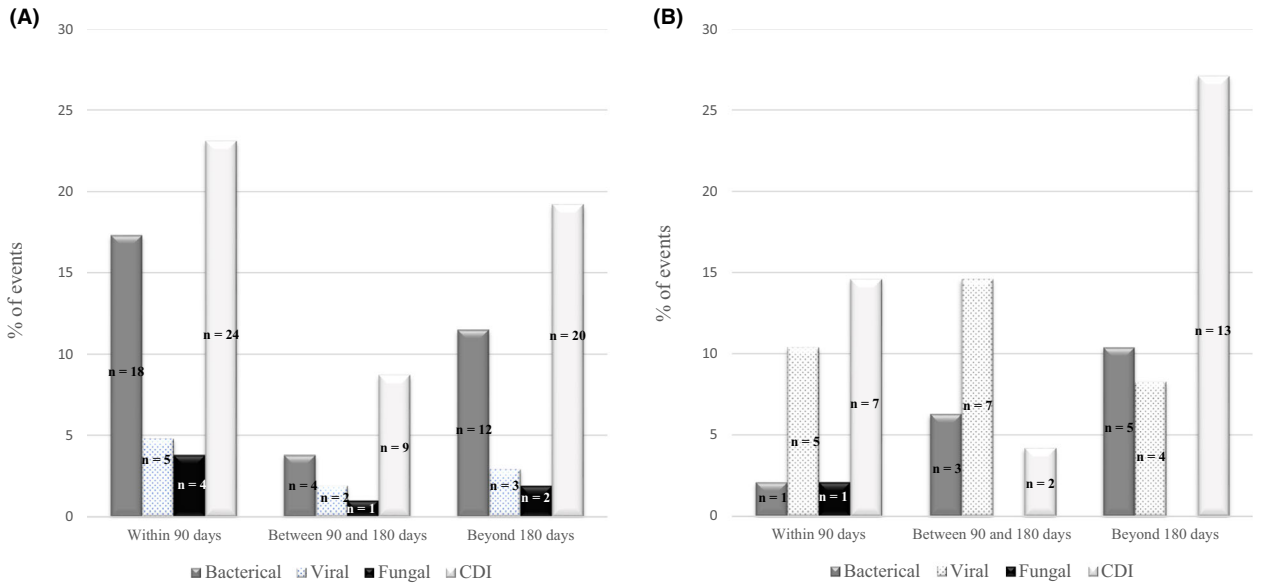

Fig 2. Rates and etiology of infections. (A) 104 infective episodes in 72 patients treated with ibrutinib; (B) 48 infective episodes in 36 patients treated with idelalisib. n indicates the number of infective episodes.

The overall rate of IFD in patients treated with ibrutinib (7/250) was not significantly higher compared to the rate in patients treated with idelalisib (1/112) (2·8% vs. 0·9%, respectively; $P = 0·25$). Lethality rate of IFD with ibrutinib was 57·1% (4 of 7 cases), not significantly higher compared to idelalisib 12·5% (1 of 8 cases) (57·1% vs. 12·5%, respectively; $P = 0·11$).

Discussion

The introduction into clinical practice of small molecules and immunotherapeutic agents for molecular targeted treatment have profoundly changed the landscape of antineoplastic therapy in haematology. In this retrospective study, we aimed to focus on the role of ibrutinib and idelalisib in the development of opportunistic infections in patients with lymphoproliferative diseases treated in clinical practice in Italy.

Our experience in a real-life setting confirms that the incidence of infections in patients treated with these agents is not negligible and has to be considered a not-uncommon "off target" effect.

Demographic and clinical characteristics of our cohort are typical for an unselected population of patients with lymphoproliferative diseases. The majority of patients (84·3%) were affected by CLL and the overall rate of infection at patient level was 29·8% (108/362) comparable to what has been reported by other authors.[5-9] In a retrospective study with 263 CLL patients, ibrutinib was associated with an increased risk of major infection, compared to the chemoimmunotherapy group (incidence rate ratio 2·35, 95% CI: 1·2–4·3).[13]

Indeed, a significant high risk for infection is already reported in clinical trials with ibrutinib for patients with relapsed disease.[10] In our study, 86% of patients treated with ibrutinib were affected by CLL and more than 40% were heavily pretreated, indicating that, in this real-life experience, ibrutinib was mainly used in the relapsed and refractory setting.

Pneumonia is the most common serious infectious complication reported in patients treated with ibrutinib.[6,8] However, the microbiological etiology of these infections remains unclear, and the spectrum of infections and immune defects caused by the long-term use of ibrutinib is not yet fully understood.

In our study, we confirm that, in patients who received ibrutinib, LRTI were the most frequent complications (42·3%). MDI accounted for only half of the infective events (49%), possibly because treatment was prescribed on outpatient basis and therefore information regarding infectious complications was limited. Gram negative bacteria constituted the most frequent etiology in patients who received ibrutinib. However, the overall mortality rate for bacterial infections was 0·4% (1/250), with an infection lethality rate of 2·9% (1/34).

During the first 6 months of treatment with ibrutinib, a higher infection rate is reported,[10] likely reflecting the impact of disease control with therapy.

We observed a median time to infection onset of 148 days, similar to what has been previously reported (136 days).[5] The majority of MDI (52·9%) occurred within 90 days from beginning of treatment (Fig 2), with a reduction to 13·7% between 90 to 180 days. However, the group of patients treated beyond 6 months experienced a new rise in the rate of infections (33·3%), mainly caused by bacteria (Fig 2). This evidence was rather unexpected, considering

that the percentage of neutropenic patients at the time of the infection was only 15%. We can therefore speculate that, with ibrutinib, although serum immunoglobulin levels are not reduced in the short term,[10,26] humoral or cellular defects may contribute to impairing antibacterial functions.

Viral infections during ibrutinib accounted for 20% of episodes and all patients recovered.

A study of 378 lymphoma patients who received ibrutinib revealed serious infections in 43 patients (11%), mostly during the first year of therapy. Invasive fungal infections were noted in 16 of these patients.[5]

In our study, the overall rate of IFD was 2·8% (7/250) and IFD represented 6·7% of total infections.

We observed five cases of IPA and one case of IA of CNS, confirming that LRTI and CNS are frequent sites of fungal involvement in patients receiving ibrutinib.

Therefore, our data from clinical practice confirm that the incidence of IFD is relatively low and support the notion that extensive routine antifungal prophylaxis is not justified in patients treated with ibrutinib. This observation is of particular relevance due to the problematic issue of potential drug interactions with use of azoles in this context. Nevertheless, we observed rare cases of IFD beyond 180 days of treatment, suggesting that close monitoring is advisable at later times.

As far as compliance to treatment, in 48% of infective episodes (50/104) the recovery was obtained without ibrutinib suspension, while in 37·5% of cases (39/104) ibrutinib was temporarily suspended and in only 14·4% of cases (15/104) was it discontinued.

Although the total discontinuation rate was rather low, it was mainly due to IFD (71%), confirming that fungal infections can significantly jeopardise treatment opportunities for these patients.

In early studies of the use of idelalisib as monotherapy or in combination with rituximab, severe infection rate was reported to be around 20%,[27] and infectious complications were considerably fewer and less severe in treatment-naïve compared to relapsed/refractory patients.[12]

The vast majority of patients who received idelalisib were affected by CLL (80·6%) and were mainly pretreated (52·8%), confirming that idelalisib also was largely used in refractory/relapsed cases. We observed an overall infection rate of 32·1% (36/112) for a total of 48 episodes, with a rate of severe infections of 50% (24/48).

The use of idelalisib is reported to be associated with rates of neutropenia up to 30%.[28] In our cohort at time of infection, 14% of patients were neutropenic and 11% were lymphopenic. It is therefore unclear if neutropenia and lymphopenia can significantly contribute to the increased infection risk. In this group of patients, we can not exclude other possible contributors to the risk of infections like the use of steroids in case of idelalisib immune-related side effects.

In our patients who received idelalisib, LRTI constituted the most frequent complications (37·5%), suggesting that, with idelalisib, diagnosis can be challenging considering the frequent pulmonary autoimmune adverse events such as pneumonitis.

In our study, CMV and/or EBV reactivations constituted 18·8% of infections (9/48) reinforcing the need for robust surveillance systems to detect reactivation of latent viruses early.

Cases of PJP emerged in early studies of idelalisib[27,29] and increased risk of opportunistic infections continued to be observed in studies of idelalisib in combination with bendamustine and rituximab.[20,30]

We observed only one case of PJP, which occurred within 90 days from starting idelalisib in combination with rituximab. Notably, this patient was not receiving anti-PJP prophylaxis, which is now considered mandatory.

Median time of first infection onset was 5·8 months from starting idelalisib and 73·1% of MDI (19/26) occurred after 90 days from beginning of treatment. This later occurrence of infections, compared to the group of patients treated with ibrutinib, might be related to the different etiological pattern with a higher number of viral infections beyond 90 days, which occurred with idelalisib.

Although our two groups of patients are not directly comparable, we observed a higher incidence of bacterial infections in patients who received ibrutinib, while the rate of viral infections/reactivations in patients treated with idelalisib was significantly higher compared to those who received ibrutinib, confirming that, with idelalisib, monitoring strategies are mandatory, as already suggested by most international guidelines.

IFD accounted for 10·3% of MDI, and this high rate has to be underlined considering that all cases of IFD were considered proven. However, the overall rate of IFD did not significantly differ between patients treated with the two agents.

The overall mortality rate for IFD in patients treated with ibrutinib was 1·6% (4/250), with a worrisome lethality rate of 57·1% (4/7). This observation suggests a unique role of BTK inhibition in the innate fungal immunosurveillance.

Furthermore, our data show that IFD is the only risk factor influencing infection mortality in patients who receive ibrutinib, thus confirming that fungal infections must be considered the most lethal complication in these highly vulnerable patients.

There are several important limitations of our study. As a retrospective study, episodes of infection were not rigorously assessed and treated uniformly. The majority of these patients were treated as outpatients, in general practice, and this could also lead to missed events.

Lastly, only patients with infections were included in the study and therefore we could not compare this cohort with the population of patients treated with the same drugs who did not experience any infective episodes.

Despite these limitations, this real-life experience confirms that the incidence of infections in patients treated with these agents is not negligible, and that bacteria are the most frequent cause of infections in patients who received ibrutinib, while

viruses are most frequently involved in patients treated with idelalisib.

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Conflicts of Interest

All other authors report no potential conflict.

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