EVALUATION OF RISK FACTORS FOR INFECTION AMONG PATIENTS RECEIVING IBRUTINIB

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BACKGROUND

- Ibrutinib is a small-molecule inhibitor of Bruton tyrosine kinase (BTK) approved for various B-cell malignancies and cGVHD[1].
- Rates of serious infection—defined as requiring hospitalization or parenteral antimicrobials— and invasive fungal infection (IFI) in patients on ibrutinib are as high as 11.4% and 4.2% respectively[2], which may be related to off-target inhibition of interleukin-2-inducible T-cell kinase or macrophage function.
- The aim of this study was to quantify the rates of infection among patients receiving ibrutinib, identify risk factors, and determine the target population in whom primary prophylaxis may be warranted.

METHODS

- We retrospectively reviewed infection complications in patients receiving ibrutinib at our institution between 06/01/2014 and 08/31/2019, including patients who received single-agent or combination ibrutinib.
- Serious infection was defined as above, or a diagnosis of pneumonia (PNA) regardless of hospitalization or parenteral antimicrobial therapy.
- Corticosteroid use was defined as prednisone 20 mg equivalent or greater for at least 4 weeks.
- For infection endpoints, patients were followed from ibrutinib initiation to three months after discontinuation. Mortality endpoints were followed through last known follow-up.

BASELINE CHARACTERISTICS

Table 1. Baseline Characteristics, N=132	n (%)
Age, median (SD), y	71 (11)
Male	103 (78)
Indication	
Chronic lymphocytic leukemia (CLL)	89 (67)
Mantle cell leukemia (MCL)	16 (12)
Waldenstrom macroglobulinemia (WM)	11 (8)
Chronic graft-versus-host disease (cGVHD)	7 (5)
Marginal zone lymphoma (MZL)	2 (2)
Small lymphocytic leukemia (SLL)	1 (1)
Other	6 (5)
Diffuse large B-cell lymphoma	3
Primary CNS lymphoma	3
Initial ibrutinib dose	
140 mg	5 (4)
280 mg	2 (2)
420 mg	105 (80)
560 mg	18 (14)
840 mg	2 (2)
Cancer treatments or immunosuppressants concurrent or w/in 3 months prior to ibrutinib initiation	
Ibrutinib monotherapy	75 (57)
In combination with rituximab-containing regimen	30 (23)
In combination with selinexor	9 (7)
In combination with other agents	18 (14)
Corticosteroid use	11 (8)
Prior hematopoietic stem cell transplant (HSCT)	
None	111 (84)
One – autologous (auto-HSCT)	11 (8)
One – allogeneic (allo-HSCT)	9 (7)
Two – both allogeneic	1 (1)

RESULTS

Figure 1. Rate of Serious Infection

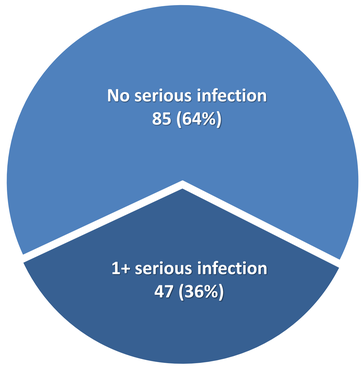
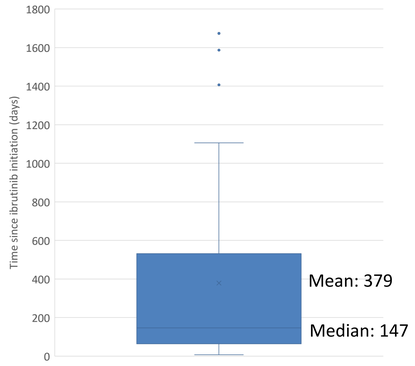


Figure 2. Time to First Serious Infection



- When pneumonia is excluded as a criteria for serious infection, rate of serious infection decreases to 27%.

Figure 3. Identified Organisms in Serious Infection

Other implicated organisms, 1 incident each

Bacterial
- *S. epidermidis*
- *P. mirabilis*
- *Neisseria spp.*
- *S. mitis*
- *C. freundii*
- *B. fragilis*
- *A. baumanii*

Viral
- RSV
- CMV
- Parainfluenza
- Varicella zoster
- Not identified – presumed viral

Fungal
- *Aspergillus spp*
- Filamentous fungus, unknown speciation

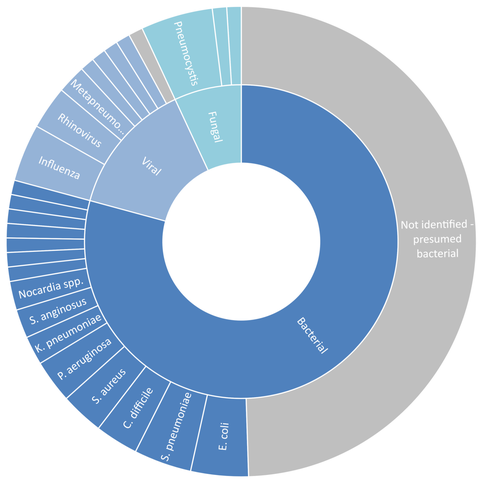
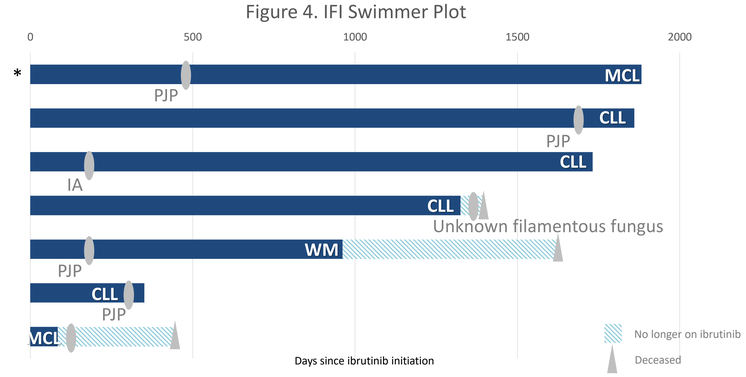


Table 2. Risk Factor Analysis	Serious Infection (excluding PNA)		Invasive Fungal Infection (IFI)	
Parameter	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Age	1.00 (0.97 – 1.04)	0.86	1.01 (0.94 – 1.08)	0.84
Indication: CLL	0.77 (0.36 – 1.65)	0.51	0.62 (0.13 – 2.94)	0.55
Initial ibrutinib dose	1.00 (1.00 – 1.00)	0.32	1.00 (0.99 – 1.01)	0.85
Diabetes	1.02 (0.41 – 2.53)	0.96	1.77 (0.32 – 9.72)	0.51
COPD	1.38 (0.30 – 6.44)	0.68	3.30 (0.34 – 32.0)	0.3
Autoimmune disorder	1.07 (0.20 – 5.78)	0.93	N/A	
Prior auto-HSCT	0.56 (0.12 – 2.77)	0.48	N/A	
Prior allo-HSCT	**4.60 (1.22 – 17.4)**	**0.02**	2.14 (0.23 – 19.8)	0.50
Concurrent cancer tx or within 3 months	1.07 (0.50 – 2.32)	0.86	3.51 (0.66 – 18.8)	0.14
Corticosteroid use	**5.55 (1.52 – 20.3)**	**0.01**	5.16 (0.87 – 30.4)	0.07

Table 3. Admission and Mortality, N=132	Result
Patients hospitalized due to infection, n (%)	34 (26)
Discrete hospitalizations	50
Median duration of hospitalization (days)	4 (Range: 1-26)
Patients admitted to intensive care unit (ICU), n (%)	10 (8)
Discrete admissions to ICU	11
Median duration of ICU admission (days)	2 (Range: 1-19)
Deceased as of last follow-up, n (%)	25 (19)
Deceased due to infection, n (%)	11 (8)
Deceased due to infection within 3 months of ibrutinib, n (%)	6 (5)

Figure 4. IFI Swimmer Plot



- Invasive fungal infection developed in 7 patients (5%).
- At the time of diagnosis, none of these patients were receiving PJP or fungal prophylaxis. One patient (indicated by asterisk) received allo-HSCT 397 days prior to ibrutinib initiation.
- All invasive fungal infections (IFI) were classified as probable by EORTC/MSG 2019 guidelines[4].

CONCLUSIONS

- Serious infection occurred at a higher rate than previously reported in the literature, with IFI rates similar to those previously described.
- Prior allo-HSCT and concurrent steroid use were found to be risk factors for serious infection.
- Treating physicians should have a high index of suspicion for pneumonia and IFI in patients receiving ibrutinib.

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4) De Pauw B, et al. "Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infectinos Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group." *Clin Infect Dis* 2008;46(12):1813-1821.

DISCLOSURES

The authors have no relevant conflicts of interest to report.

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