Investigation of Risk Factors Associated with Serious Bacterial, Viral and Invasive Fungal Infections in Hematologic Patients on Ibrutinib

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Background

- Ibrutinib is a small molecule inhibitor of Bruton's tyrosine kinase that targets B cells and is used to treat hematologic malignancies including Chronic Lymphocytic Leukemia (CLL), Non-Hodgkin Lymphoma (NHL), and Chronic Graft Versus Host Disease (GVHD). [1]
- Ibrutinib is considered to be non-myelosuppressive, however increased risk of infection including URIs, pneumonia, cellulitis and sepsis have been previously documented. [1-3]
- Numerous recent case reports and case series have suggested an increased risk of invasive fungal infections (IFI) including CNS and pulmonary aspergillosis, cryptococcosis and *Pneumocystis* pneumonia in patients on ibrutinib. [4]
- In a previous single center study of 378 patients with hematologic malignancy on ibrutinib, serious infection and IFI occurred in 11% and 4% of patients, respectively, and these were more common in patients who had 3 or more prior chemo regimens, neutropenia, or concurrent steroid use. [5]
- The aim of our study was to determine the incidence of serious infection and IFI in our hospital system in patients on ibrutinib and to determine additional risk factors in these patients.

Methods

- A retrospective analysis of all patients with hematologic malignancies prescribed ibrutinib for ≥ 1 week at Yale New Haven Hospital from July 1, 2014 to July 1, 2019 was performed.
- Demographic, clinical, and oncologic data was collected through electronic medical record review, as was Eastern Cooperative Oncologic Group (ECOG) performance score, a measure of functional status on a scale of 0-5.
- Among these data concurrent steroid use was defined as at least 14 days of ≥10 mg prednisone (or equivalent), neutropenia was defined as absolute neutrophil count ≤ 500/uL and lymphopenia as absolute lymphocyte count ≤ 400/uL.
- Patients with serious infections were defined as having (1) supporting culture data and/or imaging consistent with infection and (2) requiring inpatient management.
- IFI was defined as proven or probable based on criteria from the Mycoses Study Group Education and Research Consortium. [6]
- GraphPad Prism8 software was used for figure preparation and statistical analyses, and all tests were two tailed with statistical significance defined as a p value less than 0.05.
- Univariate analyses were performed with unpaired t tests for continuous variables and with Fisher's Exact tests for categorical variables.
- Logistic regression was performed for multivariate analyses on variables found to be significant with univariate analysis.

Results

Table 1. Baseline characteristics of patients

Total Infected (n=46)	Bacterial Infection (n=41)	Viral Infection (n=10)	Invasive Fungal Infection (n=5)	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
	21 Pneumonia, 13 UTI, 12 Bacteremia, 4 SSTI, 4 other	8 Respiratory (HMPV, PIV, Rhino, RSV), 2 Localized VZV, 1 Influenza, 1 CMV viremia	Overall	Pulmonary Cryptococcus, Proven by path	Pulmonary Aspergillosis, Proven by culture and path	Pulmonary Aspergillosis, Proven by culture and marker	Pulmonary Aspergillosis, Probable by fungal marker	Pulmonary Aspergillosis, Probable by culture
Mean Age (SD)	76.3 (11.2)	67.5 (10.6)	74 (8)	77	68	66	73	86
Female sex	34.1	20	20	No	No	Yes	No	No
Caucasian	87.8	90	100	Yes	Yes	Yes	Yes	Yes
ECOG 2 or greater	24.4	0	40	Yes	No	No	Yes	No
CLL	53.7	50	40	No*	Yes	No*	Yes	No*
Prior Chemo regimens	80.5	90	60	Yes	No	Yes	No	Yes
Mean Weeks on Ibrutinib (SD)	55.8 (63.4)	55.5 (89.1)	50.4 (64.3)	70	15	8	4	155
Max Ibrutinib Dose 560 mg	9.8	20	40	Yes	No	Yes	No	No*
Concurrent chemotherapy	9.8	20	20	No	No	Yes**	No	No
Concurrent steroid use	24.4	20	60	No	No	Yes	Yes	Yes
Neutropenia	7.3	0	0	No	No	No	No	No
Lymphopenia	9.8	10	0	No	No	No	No	No
Hypogammaglobulinemia	31.7	40	20	No	No	No	No	Yes
Prior Stem Cell Transplant	14.6	20	20	No	No	Yes	No	No
Anti-bacterial Prophylaxis	2.4	0	0	No	No	No	No	No
Anti-fungal Prophylaxis	0	0	0	No	No	No	No	No
Anti-pneumocystis Prophylaxis	12.2	30	0	No	No	No	No	No

Table 1: Data taken at time of infection, with overall averages or percentage of total reported, or individual data for each patient with IFI. SD= standard deviation. *= Mantle Cell Lymphoma; **= Cytarabine and Thiotepa

Figure 1. Infectious burden on Ibrutinib

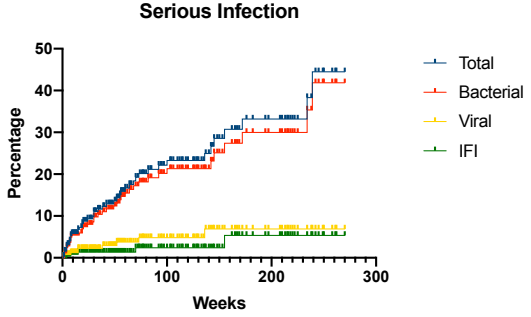

Figure 1: Percentage of patients experiencing a serious infection out of total patients remaining on ibrutinib at a given time point

Table 2. Comparison of Infected versus Uninfected Patients

Characteristics	Uninfected (n=208)	Infected (n=46)	P value, Univariate (Multivariate)	OR (95% CI)
Mean Age (SD)	71.1 (12.1)	76.7 (10.9)	**0.0045 (0.016)**	**NA**
Female sex	42.3	30.4	0.14	0.6 (0.30 to 1.2)
Caucasian	88.4	87	0.81	0.91 (0.37 to 2.3)
ECOG 2 or greater	6.7	30.4	**<0.0001 (0.0009)**	**7.0 (2.9 to 15.9)**
CLL	64.4	52.2	0.13	0.60 (0.31 to 1.2)
NHL	31.7	43.4	0.35	0.54 (0.20 to 1.5)
GVHD Post Stem Cell Transplant	3.8	4.3	>0.99	1.1 (0.24 to 4.9)
3+ Prior Chemotherapy Regimens	12	21.7	0.098	2.0 (0.90 to 4.5)
Mean Weeks on Ibrutinib (SD)	74.9 (71.5)	91.5 (83)	0.17	NA
Max Ibrutinib Dose 560 mg	7.2	19.6	0.021 (0.24)	3.1 (1.3 to 7.7)
Concurrent Chemotherapy	9.1	10.9	0.78	1.2 (0.47 to 3.4)
Concurrent Steroid Use	10	30.4	**0.0014 (0.029)**	**3.9 (1.8 to 8.3)**
Neutropenia	5.3	19.6	**0.0035 (0.045)**	**4.4 (1.8 to 11.3)**
Lymphopenia	9.1	21.7	0.022 (0.21)	2.8 (1.2 to 6.1)
Hypogammaglobulinemia	20.2	32.6	0.079	1.9 (0.90 to 3.8
Prior Stem Cell Transplant	7.7	13	0.25	1.8 (0.70 to 4.7)

Table 2: Data taken at time of ibrutinib discontinuation or last encounter prior to 7/1/2019, with overall averages or percentage of total reported. SD= standard deviation, OR= Odds Ratio. Bolded= statistically significant by multivariate analysis

Results

- Out of 246 hematologic patients on ibrutinib, 46 were found to have serious infections (18% of total), of which 5 of these had IFIs (2% of total).
- The absolute fraction of patients on ibrutinib who had experienced at least one serious infection increased steadily over time with 45% having experienced any serious infection and 5.4% having experienced IFI at 270 weeks of treatment, respectively
- Univariate statistical analysis demonstrated that infected patients were at statistically significant increased odds of having ECOG performance score ≥2 (OR 7.0), maximal ibrutinib dose of 560 mg (OR 3.1), concurrent steroid use (OR 3.9), neutropenia (OR 4.4), lymphopenia (OR 2.8), and significantly increased age.
- Multivariate statistical analysis confirmed that in infected patients there were statistically significant increased odds of ECOG performance score ≥2, concurrent steroid use, neutropenia and significantly increased age.

Conclusions

- The overall incidence of serious infections in this cohort was higher than previously reported (18% versus 11%) and the incidence of IFI was lower (2% versus 4%). However the likelihood of infection increased steadily beyond these rates in patients on ibrutinib for more than a year.
- Advanced age, high ECOG performance score, steroid use and neutropenia were the most reliable predictors of serious infections in patients on ibrutinib.
- Of the patients in our cohort who developed IFI, 4 of 5 had risk factors including elevated ECOG performance score and/or concurrent steroid use, and none were on anti-fungal prophylaxis.
- Based on these findings, patients who are elderly or frail, neutropenic, or on concurrent steroids and receiving long-term ibrutinib may be candidates for anti-microbial prophylaxis.

References

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