Increased Risk of Serious Infections in Mantle Cell Lymphoma Versus Other Hematologic Malignancies in Patients on Ibrutinib

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Background

- Ibrutinib is a small molecule inhibitor of Bruton's tyrosine kinase that has been approved for treatment of hematologic malignancies including Chronic Lymphocytic Leukemia (CLL) and Non-Hodgkin Lymphoma (NHL), and Chronic Graft Versus Host Disease (GVHD). [1]
- Ibrutinib targets B cells and is generally thought to be less immunosuppressive than other first line treatment of hematologic malignancies, however an increased risk of serious infection including bacterial, viral and fungal infections has been documented. [1-3]
- There has been particular concern regarding increased risk of invasive fungal infections (IFI) including CNS and pulmonary aspergillosis, cryptococcosis and *Pneumocystis* pneumonia in patients on ibrutinib. [4]
- IFI have been documented in patients on ibrutinib for treatment of CLL and various NHLs including Waldenstrom's Macroglobulinemia (WM), Mantle Cell Lymphoma (MCL) Diffuse Large B Cell Lymphoma DLBCL), Primary CNS Lymphoma (PCNSL), Marginal Zone Lymphoma (MZL) and Follicular Lymphoma. [4, 5]
- The aim of our study was to compare the incidence of serious infection and IFI in patients on ibrutinib for various different malignancies and to additionally determine risk factors that may make one patient population more susceptible than another.

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 defined as those with supporting culture data and/or imaging requiring inpatient management were identified.
- 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 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. Infection rates in different malignancies

Characteristic	Total (n=254)	CLL (n=158)	WM (n=35)	MCL (n=20)	DLBCL (n=6)	MZL (n=6)	Other NHL (n=19)*	GVHD (n=10)
Total Infection	18.1 (46)	15.2 (24)	11.4 (4)	50 (10)	16.7 (1)	16.7 (1)	19.1 (4)**	20 (2)
Bacterial Infection	16.1 (41)	13.9 (22)	8.6 (3)	40 (8)	16.7 (1)	16.7 (1)	19.1 (4)**	20 (2)
Viral Infection	3.9 (10)	3.2 (5)	5.7 (2)	10 (2)	0 (0)	0 (0)	0 (0)	10 (1)
Invasive Fungal Infection	2 (5)	1.3 (2)	0 (0)	15 (3)	0 (0)	0 (0)	0 (0)	0 (0)

Table 1: Infection expressed as percentage of column total with absolute number in parentheses. *= 4 lymphocytic lymphoma, 3 follicular lymphoma, 2 PCNSL, 1 lymphoid granulomatosis, 9 prolymphocytic/undefined. **= 1 PCNSL, 3 prolymphocytic/undefined.

Table 2. Baseline characteristics of patients with MCL versus other hematologic malignancies

Characteristics	Non-Mantle Cell (n=234)	Mantle Cell (n=20)	P value, Univariate (Multivariate)	OR (95% CI)
Mean Age (SD)	71.9 (12.3)	75.4 (7.6)	0.19	NA
Female sex	40.9	30	0.48	0.60 (0.20 to 1.5)
Caucasian	88	90	>0.99	1.2 (0.31 to 5.6)
ECOG 2 or greater	9.4	30	0.025 (8.5)	3.6 (1.2 to 10.5)
Prior Chemotherapy	68.4	95	0.0099 (0.74)	8.8 (1.5 to 93)
Mean length of Ibrutinib treatment in wks (SD)	79.6 (74.1)	57.2 (69.3)	0.109	NA
Max Ibrutinib Dose 560 mg	4.3	70	**<0.0001 (<0.0001)**	**52.3 (15.4 to 154)**
Concurrent chemotherapy	6	35	**0.0004 (0.012)**	**8.5 (3.1 to 22.9)**
Concurrent steroid use	12.4	30	0.041 (0.17)	3 (1.1 to 8.2)
Neutropenia	7.3	15	0.20	2.3 (0.60 to 7.7)
Lymphopenia	10.3	25	0.062	2.9 (1.1 to 8.6)
Hypogammaglobulinemia	22.2	25	0.78	1.2 (0.40 to 3.1)
Prior Stem Cell Transplant	6.4	35	0.0005 (0.079)	7.9 (2.9 to 20.8)
Total Infection	15.4	50	**0.0007 (0.0099)**	**5.5 (2.0 to 14.8)**
Bacterial Infection	14.1	40	0.0067*	4.1 (1.5 to 10.5)
Viral Infection	3	10	0.18	3.1 (0.63 to 15)
Invasive Fungal Infection	0.9	15	0.0038*	20.5 (3.8 to 118)

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. Bold connotates statistically significant by multivariate analysis. *= not included in multivariate analysis.

Figure 1. Characteristics of patients with MCL versus other hematologic malignancies

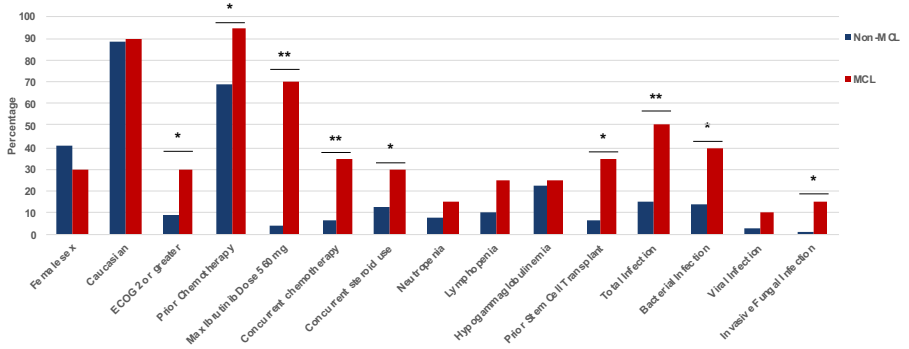

Figure 1: Comparison of percentage of all MCL to those with other hematologic malignancies. *= statistically significant by univariate analysis, **= statistically significant by multivariate analysis.

Results

- Out of 246 patients, 46 total experienced one or more serious infections (18.1%), with 42 experiencing bacterial infections (16.1%), 10 experiencing viral infections (3.9%), and 5 experiencing IFI (2%).
- In comparison to all other malignancies, MCL patients (n=20) experienced a higher proportion of total infections (50%), bacterial infections (40%), viral infections (20%) and IFI (15%)
- Univariate statistical analysis demonstrated statistically significant increased odds of MCL patients with ECOG performance score ≥2 (OR 3.6), on a maximal ibrutinib dose of 560 mg (OR 52.3), with concurrent chemotherapy (OR 8.5), with prior chemotherapy (OR 8.8), with concurrent steroid use (OR 3), with prior stem cell transplant (OR 7.9), and experiencing at least one serious infection (OR 5.5), bacterial infection (OR 4.1) or IFI (OR 20.5).
- Multivariate statistical analysis confirmed statistically significant increased odds of MCL patients on maximal ibrutinib dose of 560 mg, with concurrent chemotherapy, and experiencing at least one serious infection.

Conclusions

- A greater proportion of MCL patients experienced serious infections than with any other hematologic malignancy, and 3 of 5 cases of IFI in this cohort occurred in MCL patients
- Factors that may have predisposed MCL patients to a greater risk of IFI and other serious infections may include a higher likelihood of a maximal ibrutinib dose of 500 mg, concurrent or prior chemo, ECOG performance score of 2 or greater, concurrent steroids, and prior stem cell transplant.
- Based on these findings it may be advised that MCL patients started on ibrutinib at the maximal dose of 560 mg with or without concurrent chemotherapy should be monitored closely for serious infection and considered for antimicrobial prophylaxis.

References

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