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The Impact of BTK Inhibitors on COVID-19 Outcomes in Patients with Chronic Lymphocytic Leukemia: A real-world study in the Omicron wave

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INTRODUCTION

- In May 2023, the World Health Organization (WHO) declared Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is no longer a "global health emergency," despite the continuing global threat. The Omicron variant led to higher infection rates, increased transmissibility, and reduced vaccine efficacy.
- The Omicron variants BF.7, BA.5.1, and BA.5.2 became predominant in Beijing, China, with a significant resurgence of BF.7 variant since late September 2022. [1]
- A prospective phase II trial found no significance of ibrutinib in severe COVID-19. [2]
- The European Research Initiative on CLL (ERIC) reported that CLL patients with severe COVID-19 under BTKis had a lower rate of hospitalization than patients treated with other strategies. [3] The other international study involving CLL patients with COVID-19 infection showed similar fatality rates and survival in patients with and without BTKi. [4]
- Whether continuous BTKi treatment is a favorable or poor risk factor for CLL patients needs to be determined.

OBJECTIVE(S)

- We aimed to explore the impact of BTKi treatment on the occurrence and severity of COVID-19 in CLL patients in the Omicron epidemic.

METHOD(S)

- This single-center, retrospective study was conducted on CLL patients diagnosed and regularly followed up at Peking University Peoples' Hospital. Patient data were obtained through telephonic visits, ensuring adherence to COVID-19 safety measures and minimizing the risk of exposure for patients and healthcare providers from March 15, 2023, to April 1, 2023.
- COVID-19 occurrence was determined as any respiratory infection symptom and laboratory evidence of SARS-Cov-2, either positive nucleic acid PCR or positive antigen detection.
- Severe COVID-19 was defined as dyspnea, respiratory rate of ≥30/min, a blood oxygen saturation of ≤93%, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO2:FIO2) of <300 mm Hg, or infiltrates in >50% of the lung field. [5]

RESULT(S)

Patients' characteristics

- Overall, 151 CLL patients registered from November 15, 2022, to January 20, 2023 were included in the study.
- A total of 117 (77.5%) patients were administered different BTKi treatments with ibrutinib being the most common BTKi received (n=68; 58.1%) followed by zanubrutinib (n=30; 25.6%), acalabrutinib (n=11; 9.4%) and orelabrutinib (n=8; 6.8%). The median duration of exposure to BTKi varied across the different treatments. The longest duration of exposure was observed for orelabrutinib (46 months, range: 10-49) followed by ibrutinib (39 months, range: 4-104), zanubrutinib (25 months, range:4-63) and acalabrutinib (20 months, range: 14-24).
- 34 patients were not under CLL treatment.
- 17 (50%) were vaccinated against COVID-19 whereas in BTKi treatment group only 21 of 117 (17.9%) were vaccinated (P<0.001).
- No patient reported any previous exposure to SARS-Cov-2 and previous COVID-19.

RESULT(S)

COVID-19 occurance

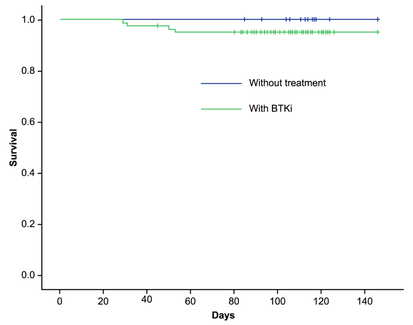
- A total of 112 (74.2%) CLL patients suffered from COVID-19. The patients receiving BTKi treatment and those without treatment exhibited similar COVID-19 incidence (CLL with BTKi: 74.4% [n=87] compared with CLL without treatment: 73.5% [n=25], P=0.923)
- Five (5.7%) CLL patients with COVID-19 in the BTKi treatment group were admitted to the ICU and four died. No ICU admissions and mortality were in patients without CLL treatment (Table 1).

Table 1. Comparison of risk factors and COVID-19 occurrence between BTKi and no-treatment groups

Risk factors	BTKi N=117	No treatment N=34	P value
Male, n (%)	71 (60.7)	22 (64.7)	0.671
Age <65 years, n (%)	39 (33.3)	13 (38.2)	0.854
Age 65-75 years, n (%)	61 (52.1)	16 (47.1)	
Age ≥75 years, n (%)	17 (14.5)	5 (14.7)	
CIRS ≥7, n (%)	6 (5.1)	0 (0)	0.338
Progressive disease	3 (2.6)	1 (2.9)	1
COVID-19 vaccinated	21 (17.9)	17 (50)	<0.001
Antivirus treatment	22/87 (25.3)	3/25 (12.0)	0.16
COVID-19 disease	87 (74.4)	25 (73.5)	0.923
Hypoxemia, n (%)	39 (44.8)	4 (16.0)	0.009
ICU admission, n (%)	5 (5.7)	0	0.585
Death, n (%)	4 (4.6)	0	0.573

- The mortality rate was not significantly different as there was no event in patients without treatment (Figure 1).

Figure 1. Kaplan-Meier survival curve of CLL patients with COVID-19



RESULT(S)

Influence of BTKi on severe COVID-19

- Univariate analysis revealed that age ≥65 years (HR: 2.392; 95%CI: 1.019, 5.619; P=0.045), no vaccination (HR: 3.802; 95%CI: 1.319, 10.989; P=0.013), and treatment with BTKi (HR: 4.266; 95%CI: 1.351, 13.468; P=0.009) were significant risk factors for hypoxemia in CLL patients with COVID-19, while no significance was observed with sex, CIRS ≥7 and progressive disease.
- Multivariate analysis included all factors with a P value <0.2. It showed that continuous BTKi treatment was the only risk factor for hypoxemia in CLL patients with COVID-19 (HR: 4.220, 95%CI: 1.319, 13.504; P=0.019) (Table 2).

Table 2. Univariate and multivariable logistic regression analysis of hypoxemia.

Risk factors	Uni-variate analysis		Multi-variate analysis	
	HR [95% CI]	P value	HR [95% CI]	P value
Sex	1.292 [0.561, 2.972]	0.547		
Age≥65 years	2.392 [1.019, 5.619]	0.045	2.364 [0.983, 5.582]	0.055
CIRS≥7	0 [0, -]	0.999		
Progressive disease	1.634 [0.222,13.468]	0.630		
COVID-19 vaccination	0.263 [0.091, 0.758]	0.013	0.425 [0.134, 1.348]	0.146
BTKi treatment	4.266 [1.351, 13.468]	0.013	4.220 [1.319,13.504]	0.015

CONCLUSION(S)

Our results show that continuous use of BTKi was associated with severe COVID-19, but it does not influence COVID-19 occurrence.

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