Chronic Lymphocytic Leukemia in the SARS-CoV-2 Pandemic

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Abstract

Purpose of Review Chronic lymphocytic leukemia (CLL) is the most frequent lymphoproliferative disease in the elderly of the western world. Immune defective responses and treatment can worsen the immune system's competence of CLL patients. Consequently, they may present a higher incidence of recurrent severe infections, second malignancies, and reduced efficacy of vaccines. The outbreak of COVID-19 is an ongoing pandemic, and patients with comorbidities experience more severe forms of the disease. Hematological malignancies are associated with higher case fatality rates (CFRs) than other cancers. Knowledge about COVID-19 incidence, clinical course, and immune response to the infection and vaccination in CLL may contribute to design strategies that improve the outcomes of patients in the future.

Recent Findings The prevalence of SARS-CoV-2 positivity in CLL is not significantly higher than seen in the general population. CFRs for CLL patients are 16.5-fold more elevated than the median reported worldwide and even higher in older patients, those who require hospitalization have significant comorbidities or need oxygen therapy. CLL status decreases the anti-SARS-CoV-2 positivity after infection or vaccination by around 40%, and the spike-specific antibody titers are 74-fold lower than healthy age-matched controls. The response rate to COVID-19 vaccines is even worse in patients with active CLL-directed therapies like BTKi, BCL-2 antagonists, or anti-CD20 monoclonal antibodies.

Summary CLL patients are at a greater risk of death from COVID-19. Inherent immunosuppression of CLL and immune deficiencies caused by treatment significantly decrease the ability to produce natural or vaccine-induced anti-SARS-CoV-2 immune responses.

Keywords SARS-CoV-2 · COVID-19 · CLL · Chronic lymphocytic leukemia · Antibody · Vaccine · BTK inhibitors

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and its related disease, coronavirus disease of 2019 (COVID-19) severely affected worldwide since first detected in December 2019 in Wuhan, China [1]. COVID-19 has a heterogeneous course, ranging from asymptomatic infection or mild symptoms to a very aggressive disease with acute respiratory failure and multiorgan failure [2]. In the general population, the estimate of infection fatality rate is 0.68%, with an exponential increase with age up to 5.6% for those 65 years and older [3]. Many patients with severe forms of COVID-19 have evidence of comorbidities such as obesity, cardiovascular disease, liver disease, kidney disease, immunosuppression, or cancer [4]. In general, patients with hematological malignancies have more severe disease and a higher case fatality rate than other cancers [5]. However, patients with no active cancer (watch and wait surveillance or complete remission) presented better outcomes [6].

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in adults in countries with a predominantly Caucasian population [7]. This condition clusters many of the risk factors associated with severe forms of COVID-19, primarily affects the elderly, with the majority of patients being > 65 years of age at diagnosis [8], is associated with impaired immune function [9] that results in

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inadequate response to vaccination [10], and is treated with agents that modulate the immune system [11].

COVID-19 Incidence in CLL Patients

From the beginning of the pandemic, a relevant question was if some conditions could increase the risk of SARS-CoV-2 infection or more severe forms of COVID-19. CLL patients were of particular interest because of the intrinsic immunosuppression caused by the disease and the need for continuous treatment to obtain leukemia control.

In August 2020, Cuneo et al. reported a survey based on 9930 patients with CLL managed during the COVID-19 pandemic from 33 centers, accounting for approximately one-third of all patients in Italy. The prevalence of COVID-19 positivity in CLL was estimated at 0.5%, not significantly higher than seen in the general population. Other interesting findings were that patients experienced delays in treatment initiation or the administration of planned courses, restraints in the use of blood products, and the need for postpose restaging after treatment [12•].

Outcomes to COVID-19 in Patients with CLL

As of August 2021, the SARS-CoV-2 pandemic has resulted in 215 million infections worldwide and more than 4 million deaths from COVID-19. The median global case fatality rate (CFR) is estimated to be 1.7%, ranging from 18.8 to 0.1% [13]. Symptomatic patients of COVID-19 belong mostly to the 40–70 years age group, and the most common symptoms are fever (83.3% [95% *CI* 78.4–87.7]), cough (60.3% [54.2–66.3]), and fatigue (38.0% [29.8–46.5]). Some patients may also present myalgias, breathlessness, abdominal pain, vomiting, and diarrhea [14].

Two extensive cohort studies have characterized the clinical course of CLL patients diagnosed with COVID-19. In July 2020, the European Research Initiative on CLL (ERIC) and the CLL Campus published a retrospective international multicenter study based on a survey completed by 121 investigators from 118 sites. From 221 cases with suspected COVID-19, one-hundred and ninety (92.2%) were positive for molecular tests. Incidence of COVID-19 reported among 15,083 cases was 1.06%, and 0.9% of patients required hospitalization [15••]. Two months later, another multicenter, international cohort study was reported with data from 198 patients. Fifty percent of cases were diagnosed in the USA and 48% in Europe or the UK [16••].

With the primary goal of reporting the CFR of a large group of patients with CLL and COVID-19 and analyzing mortality trends over time, a study with 374 patients from 45 centers in the USA and Europe was published in July

2021. The analysis of all patients included 374 patients with a median follow-up of 38 days (range 1–364 days). The CFR reported was 28%, with significant differences between the patients who required hospitalization (36%) and those treated at home (4.3%). In the univariate analysis, age > 75 years and cumulative illness rating scale-geriatric (CIRS) > 6 were independent predictors of poor survival. When comparing two cohorts, investigators found that patients treated from February to April 2020 required hospital (85% vs. 55%) and ICU admission (32% vs. 15%) more frequently with a higher CFR when compared with patients treated from May 2020 to February 2021. The CFR for patients requiring hospitalization and oxygen therapy was also higher in the patients treated after May 2020, and the proportion of BTK inhibitor (BTKi) hold or discontinuation was reduced over time [17••].

Data shown in Table 1 compares age, comorbidities, CLL treatment status at the time of COVID-19 diagnosis, and admission requirements of the three cohorts previously mentioned. The age at COVID-19 diagnosis was very uniform, consistent with the typical prevalence of CLL in the elderly. The frequency of comorbidities was similar between Scarfo and Mato reports, with a greater proportion of hypogammaglobulinemia in the ERIC experience. Interestingly, the proportion of patients that received CLL treatment previously or were untreated at the time of COVID-19 diagnosis was the same in the Scarfo and Mato experience, in contrast with the Roeker cohort that reported a more significant proportion of untreated patients. The CLL treatment used more frequently was BTKi in close to one-third of the patients; the second preferred regimen was venetoclax, with less than 10% in all the cohorts.

Presenting symptoms in patients with CLL diagnosed with COVID-19 are shown in Table 2. All symptoms of COVID-19 were more frequent in the study of Mato et al., except for hyperthermia, which was present in nearly the same proportion in two cohorts of CLL patients. In order to compare the clinical course of CLL patients with the general population, Table 2 includes data of a different group of adults with a median age of 77.5 years, very similar to CLL patients [18]. The only symptom that was noticeably different was the fever, being more prevalent in leukemia patients.

Impact of CLL Diagnosis in the Immune Response to SARS-CoV-2 Vaccination

B cells produce antibodies in response to viral infection or vaccination. Antibodies constitute the first line of defense against viral diseases. Neutralizing antibodies produced by exposure to the virus or vaccination protect against new infections blocking virus entry into host cells. Their measurement in plasma is a valuable tool to determine

Table 1 Comparison of patient baseline characteristics

n	Scarfo et al. July 2020 [15••]	Mato et al. September 2020 [16••]	Roeker et al. July 2021 [17••]
	190	198	374
Median age at COVID-19 diagnosis (range)	72 (48–94)	70.5 (38–98)	68 (29–98)
Comorbidities			
Hypertension	54%	51%	
Diabetes mellitus	24%	20%	
COPD	6%	11%	
Cardiovascular	29%	33%	
Hypogammaglobulinemia	57.8%	44%	
Other	26%	33%	
CLL treatment history			
Previously untreated	39%	39%	45%
Prior therapy	61%	61%	55%
CLL therapy at COVID-19 diagnosis	34%	45%	38%
BTK inhibitor	23.2%	30.8%	26%
Venetoclax based	4.7%	7%	8%
PI3K inhibitor-based	1.6%	1%	
Bendamustine + rituximab	1%	0.5%	
Other	2.1%	6%	
COVID-19 management			
Hospitalization	68.4%	90%	75%
ICU admission	20.5%	35%	27%

Table 2 Clinical presentation of CLL patients with COVID-19

	CLL cohort Scarfó et al. July 2020 [15••]	CLL cohort Mato et al. September 2020 [16••]	Elderly population Kerr et al. November 2020 [18]
Fever	87%	88%	57%
Cough	49%	85%	51.3%
Dyspnea	48%	74%	53%
Myalgias/arthralgias	15%	36%	
Nausea and vomiting	3%	14%	13.9%
Diarrhea	12%	29%	16.5%
Fatigue	17%	72%	27.8%
Sore throat	4%	16%	

response to infections and efficacy of vaccines [19]. IgG anti-SARS-CoV antibodies are detected in 95.3% of COVID-19 patients 5 weeks after symptom onset. A delay in IgG development is associated with a higher incidence of severe or critical disease, and the IgG levels are higher in older patients and those with more severe forms of the disease. IgG levels against spike protein (S) or the receptor-binding domain (RBD) are particularly important in viral clearance and COVID-19 recovery [20].

Serology testing in twenty-one CLL patients at a median of 55 days after diagnosis found that only 67% of patients had detectable levels of antiSARS-CoV-2 IgG antibodies. Hypogammaglobulinemia was negatively associated with antibody response, and IgG production was more frequent in CLL patients that recovered from severe COVID-19 [21].

The evidence of the ability to neutralize the SARS-CoV2 by human antibodies resulted in the development of multiple effective and safe COVID-19 vaccines at an unprecedented speed to achieve protective immunity and eradicate this pandemic. The approved vaccines have shown outstanding efficacy inducing antibody levels of similar or higher magnitude as those observed after exposure to the virus. Fully vaccinated people gain almost complete protection against hospitalization and severe disease [22].

Intrinsic immune impairment in CLL patients and CLL-directed therapy may impact the efficacy of vaccines. For example, a paper by Pleyer et al. reported a 4% response rate to the recombinant hepatitis B vaccine in patients treated with BTKi, in contrast to a 28% response rate in treatment-naïve patients. Response to the recombinant herpes zoster vaccine also was reduced by BTKi therapy [23•].

Roeker et al. analyzed the serum levels of anti-SARS-CoV-2 S1/S2 antibodies in 44 patients with CLL who received

two doses of mRNA vaccine BNT162b2 (BioNTech & Pfizer) or mRNA-1273 (Moderna & NIH, EE. UU.). Forty-one percent of patients were on treatment at the time of the vaccination, 32% with BTKi, 32% with anti-CD20 mAB, and 16% with venetoclax. CLL treatment was not held or modified before immunization. Half of the patients were positive for anti-SARS-CoV-2 S1/S2 antibodies. Antibody positivity was strongly associated with untreated CLL and age < 70 years [24•].

In another study, anti-SARS-CoV-2 S antibodies were measured from 2 to 3 weeks after the second dose of the BNT162b2 mRNA COVID-19 vaccine in 167 patients with CLL/SLL and 52 healthy control subjects. Almost one-third of CLL patients were treatment naïve, 44.9% were on CLL-directed therapy, 14.4% were on remission, and 6.0% were on disease relapse after being previously treated. Antibody response to the vaccine was present in only 39.5% of patients with CLL, in contrast to 100% in age- and sex-matched control subjects. CLL patients with a serologic response to vaccination also showed lower antibody titers than their healthy counterparts. Age < 65 years, female gender, mutated IGHV status, β2-microglobulin $\leq$ 3.5 mg/L, early disease stage, lack of active treatment, and higher serum immunoglobulin levels were all associated with higher antibody responses. CLL treatment at the time of vaccination severely impaired antibody production. The response rate to the vaccine was 16% in patients receiving BTKi, 13.6% in patients treated with venetoclax $\pm$ anti-CD20 antibodies, and absent in patients treated with anti-CD20 antibodies within the last 12 months before vaccination. Even treatment-naive patients have reduced responses and lower antibody titers than healthy individuals, presumably caused by qualitative and quantitative immune defects intrinsic to the leukemia diagnosis [25••].

Finally, a study conducted in the UK enrolled 299 CLL patients and 93 age-matched healthy donors that received either the PfizerBioNTech mRNA vaccine (51.5%) or the AstraZeneca/Oxford ChAdOx1 adenovirus vaccine (48.5%). Samples from CLL patients had a 2.8-fold lower response rate and 104-fold lower antibody titers than age-matched healthy donors following first vaccine dose. Spike-specific antibody production was particularly impaired in patients on BTKi therapy. After the second vaccination, spike-specific antibody responses were identified in 75% of samples from the patient group, but the titer was 74-fold lower than healthy age-matched controls. BTKi treatment was also a strong and independent predictor of negative antibody response after the second vaccine [26••].

Conclusion

Patients with CLL face an unprecedented adverse situation. In addition to the adverse events caused by cancer, they are at a greater risk of dying from complications related to COVID-19. According to the World Health Organization, CLL patients belong to the higher priorities on using vaccines against COVID-19, even when the efficacy of immunization in this population is very low. Vaccinated patients with CLL should continue to adhere to masking and social distancing recommendations. Research and clinician's experience must guide decisions about cancer therapy and vaccination optimization during the SARS-CoV-2 pandemic.

Declarations

Ethics Approval Not applicable.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest The authors declare no competing interests.

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•• Of major importance

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