RESEARCH LETTER

blood advances

TO THE EDITOR:

COVID-19 in patients with chronic lymphocytic leukemia treated with venetoclax: what is the role of anti-CD20 antibody?

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for coronavirus disease 19 (COVID-19), has led to a significant increase in morbidity worldwide since its outbreak.[1] Ongoing antileukemic treatment may worsen the immunological status of patients with chronic lymphocytic leukemia (CLL), possibly leading to worse outcomes of COVID-19.[2,3]

A recent meta-analysis showed a high case fatality rate in hospitalized patients with hematologic malignancies[4] and published reports indicated high rates also in patients with CLL.[5-9] Outcomes ameliorated with the introduction of new drugs against SARS-CoV-2, but a great reduction of the mortality rate was allowed by prophylaxis with the vaccines administration.[7]

Our study aimed to evaluate the impact of COVID-19 in patients with CLL treated with venetoclax based on data collected from a retrospective study conducted by the SEIFEM (Sorveglianza epidemiologica infezioni nelle emopatie) group.

The retrospective multicenter study included 258 patients with CLL treated from January 2017 to December 2022 with venetoclax single agent until progression or toxicity (122 patients) or venetoclax plus anti-CD20 antibody as fixed-duration therapy (136 patients, of whom 128 venetoclax plus rituximab and 8 venetoclax plus obinutuzumab). The median time on venetoclax was 20 months (range, 1-68); patients previously exposed to venetoclax who withdrew treatment before the onset of the pandemic in February 2020 were excluded.

In conformity with what was previously reported in other settings of immunological treatment of hematologic cancers,[10] we considered 3 different ERAs: the first period (ERA-1) spanned from the beginning of the COVID-19 pandemic until the time when SARS-CoV-2 vaccination was available (February 2020 through February 2021); the second period (ERA-2) spanned from the beginning of SARS-CoV-2 vaccination until the time when passive prophylactic measures with tixagevimab-cilgavimab became available (March 2021 through March 2022); and the third period (ERA-3) began with the initiation of passive prophylactic measures with tixagevimab-cilgavimab (from April 2022).

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The data sets used and/or analyzed during the study are available upon reasonable request from the corresponding author, Francesco Autore (francesco.autore@policlinicogemelli.it).

The full-text version of this article contains a data supplement.

The severity of COVID-19 was graded from 1 to 5 according to Common Terminology Criteria for Adverse Events (CTCAE). We then divided infections into 2 subgroups: grades 1 to 2 and grades 3 to 5. Treatment consisted of antiviral drugs (remdesivir, nirmatrelvir/ritonavir, and molnupiravir), anti-SARS-CoV-2 monoclonal antibodies, such as sotrovimab or anti-inflammatory agents with or without antibiotics, and supportive therapy when necessary. From April 2022 pre-exposure prophylaxis of the SARS-CoV-2 infection with a 150/150 mg dose of 2 long-acting anti-spike monoclonal antibodies, tixagevimab/cilgavimab, was available.[11,12]

This study was conducted according to the ethical and scientific quality standards of Good Clinical Practice (GCP). The study was approved by the institutional review board of the center (Prot N. 0034740/21 - Del 06 October 2021), and all patients signed written consent.

Data were analyzed using the NCSS 2020 Statistical Software (NCSS, LLC, Kaysville, UT).

We recorded 111 infections from SARS-CoV-2 confirmed by nasopharyngeal swab in 104 of 258 patients (40.3%), with a median time from venetoclax initiation to swab positivity of 18 months (range, 1-64). The median age of the patients with COVID-19 was 69 years, and 69% were men. The baseline characteristics of the 104 patients who experienced COVID-19 were compared with those of the 154 patients who did not experience the infection (Table 1). Patients in the first group did not show more comorbidities in terms of the Cumulative Illness Rating Scale or renal and pulmonary impairment. They received a median of a single line of therapy (vs 2 different previous lines of treatment of patients without COVID-19; $P = .02$) but more patients received venetoclax plus anti-CD20 antibody (64.4% vs 44.8%; $P = .002$). Unexpectedly, patients without COVID-19 experienced more previous non-COVID infections in the 12 months before the beginning of venetoclax (37.7% vs 21.1%; $P = .005$), but a similarly low rate of previous SARS-CoV-2 infection (5.2% vs 4.1%).

The rate of vaccination was 79.5% with a median of 3 doses for both groups; only 24.5% of the patients received pre-exposure prophylaxis with tixagevimab/cilgavimab.

When we distinguished 67 grade 1 to 2 COVID-19 (3 cases in ERA-1, 13 in ERA-2, and 51 in ERA-3) and 44 grade 3 to 5 COVID-19 (5 cases in ERA-1, 15 in ERA-2, and 24 in ERA-3) cases, we noted that anti-CD20 monoclonal antibody administration was more frequently associated with patients with grade 3 to 5 COVID-19 together with diabetes (supplemental Table 1).

The univariate analysis revealed that previous lines of treatment ($P = .035$), previous infections ($P = .005$), and association with anti-CD20 ($P = .002$) were significant risk factors for the infection; when considering only the severe COVID-19 infection, association to anti-CD20 ($P = .017$) confirmed its role together to diabetes ($P = .031$).

Multivariate analysis found that the association with anti-CD20 was an independent risk factor for COVID-19 of any grade (odds ratio, 1.75; 95% confidence interval, 1.01-3.06; $P = .046$) and diabetes for grade 3 to 5 COVID-19 (odds ratio, 11.31; 95% confidence interval, 1.35-94.4; $P = .025$).

Remdesivir was the most used antiviral alone or in combination throughout the whole period in grade 3 to 5 infections, from ERA-2 nirmatrelvir/ritonavir, increasing its use to become the most administered antiviral in grade 3 to 5 COVID-19 in ERA-3 (Figure 1).

During the COVID-19 infection, venetoclax was withdrawn in 38 (36.5%) patients, in 32 of whom (84.2%) venetoclax was administered together with anti-CD20 antibody; 25 of the 38 patients (65.8%) resumed targeted therapy. Thirty-six patients (34.6%) required hospitalization due to COVID-19: the median time of recovery was 16 days, and 8 (7.7%) patients needed intensive care unit admission.

Among the 104 patients with COVID-19, 18 patients died, and 10 deaths were due to COVID-19: 7 of 10 were exposed to anti-CD20 antibody, and none experienced a SARS-CoV-2 infection before treatment with venetoclax. Six patients were vaccinated with at least 3 doses, 3 patients were not vaccinated but were infected and died in ERA-1, and only 1 patient was not vaccinated in ERA-2.

Table 1. Basal characteristics of the 104 patients who experienced COVID-19 were compared with those of 154 patients who did not experience the infection

	Patients with COVID-19 (n = 104)	Patients without COVID-19 (n = 154)	*P* value
Age, Med (95% CI)	69 (66-70)	71 (68-71)	.222
Sex, M	69.2%	71.4%	.704
CIRS, Med	4 (3-5)	5 (4-6)	.502
Smoking, yes	14.6%	19.5%	.309
Diabetes, yes	7.7%	13.6%	.138
COPD, yes	15.4%	13.6%	.694
CrCl <70 mL/min, yes	36.5%	40.1%	.562
Previous lines of treatment, Med	1 (1-2)	2 (2-2)	.020
Previous infection, yes	21.1%	37.7%	.005
Previous pneumonia, yes	7.7%	9.8%	.571
Previous COVID-19, yes	4.1%	5.2%	.695
Association to anti-CD20, yes	64.4%	44.8%	.002
Immunoglobulin prophylaxis, yes	16.4%	22.1%	.256
PJP prophylaxis, yes	60.6%	56.5%	.514
Antiviral prophylaxis, yes	35.6%	40.9%	.388
RAI III-IV, yes	50.9%	46.1%	.443
IGHV, unmut	70.8%	70.9%	.987
Del17, yes	26.6%	31.8%	.379
TP53, yes	26.6%	36.4%	.121
Del11, yes	19.4%	26.9%	.178
Tri12, yes	10.2%	15.6%	.229
Del13, yes	27.6%	38.9%	.065
IgG, Med	585 (472-679)	600 (551-650)	.923
LDH above ULN, yes	47.6%	45.5%	.749

CI, confidence interval; CIRS, Cumulative Illness Rating Scale; COPD, Chronic Obstructive Pulmonary Disease; CrCl, Creatinine Clearance; IgG, immunoglobulin G; IGHV, immunoglobulin heavy chain variable; LDH, lactate dehydrogenase; M, male; Med, median; PJP, *Pneumocystis jiroveci* pneumonia; ULN, upper limit of normal; unmut, unmutated.

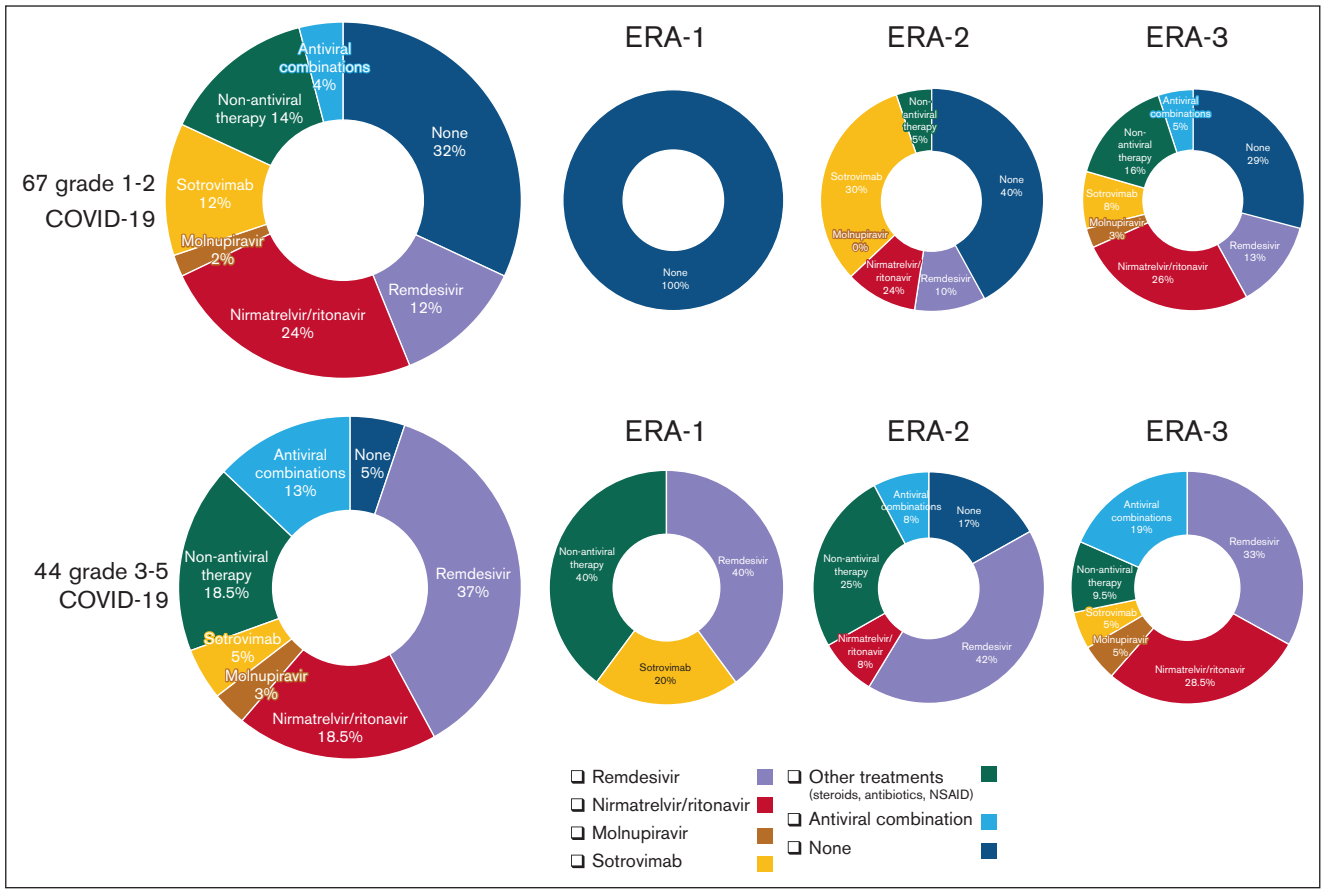

Figure 1. COVID-19 treatments according to the severity of the infection and 3 different ERAs. In COVID-19 grade 1 (G1) to G2, treatments consisted of remdesivir in 12% of the cases, nirmatrelvir/ritonavir in 24%, molnupiravir in 2%, antiviral combinations in 4%, sotrovimab in 12%, other treatments such as steroids, antibiotics, and anti-inflammatory agents in 14%, and none in 32%. In COVID-19 G3 to G5, treatments consisted of remdesivir in 37% of the cases, nirmatrelvir/ritonavir in 18.5%, molnupiravir in 3%, antiviral combinations in 13%, sotrovimab in 5%, and other treatments, such as steroids, antibiotics, and anti-inflammatory agents in 18.5%, and none in 5%. NSAID, nonsteroidal anti-inflammatory drug.

The rate of mortality due to COVID-19 was 9.6% in patients who were infected with SARS-CoV-2 but increased to 22.7% among patients with severe grade 3 to 5 COVID-19. The mortality rate strongly decreased as far as passive prophylaxis and new treatment drugs became available: from a mortality rate of 14% in ERA-1 and ERA-2, it dropped to 6.6% in ERA-3.

This real-life study of 258 patients with CLL treated with venetoclax approached patients with CLL in targeted treatments. Low rates of responses to vaccination were seen in patients treated with ibrutinib or venetoclax.[13-22]

Our epidemiological analysis found that 40% of patients were infected with SARS-CoV-2; in 60% of the cases, the infection was grade 1 to 2. We found an association between anti-CD20 antibody and venetoclax as a unique risk factor for SARS-CoV-2 infection, indicating that this treatment-related immunosuppression was a strong risk factor for overcoming others. Immunosuppression, together with impaired microvascular circulation, could be the explanation for the role of diabetes in severe COVID-19.

The use of anti-CD20 agents led to a more severe COVID-19 clinical course also in the study of Pula et al,[9] in line with an observational multicenter study performed in 941 patients with CLL, which showed that the use of anti-CD20 antibodies alone or in combination led to the shorter overall survival when compared with untreated patients.[5]

In our study, which included mainly vaccinated patients, 34.6% of patients required hospitalization due to COVID-19 and 7.7% of patients needed intensive care unit admission. In the analysis conducted by Pula et al, COVID-19 was clinically severe in a not negligible proportion of patients with a case fatality rate higher than 20%, but almost 40% when considering patients requiring hospitalization due to COVID-19 infection; in this cohort, 59% of patients required hospitalization.[9]

The rate of mortality due to COVID-19 in our study was 9.6%, but it was higher (22.7%) among patients with severe grade 3 to 5 COVID-19. Mauro et al, described 3 patients over a population of 29 patients with CLL on active treatment with venetoclax (10.3%) who died due to COVID-19.[22]

Interestingly, analysis of COVID-19–directed therapies revealed that in our casistics, remdesivir was the most commonly used antiviral with good effectiveness, and nirmatrelvir/ritonavir obtained good results, but few data are available for this drug in CLL.

Pre-exposure prophylaxis with tixagevimab/cilgavimab seemed to reduce complications of SARS-CoV-2 even if some of the pre-exposed patients required hospitalization[22]; low rates of administration did not allow for statistical analysis.

Considering the variable drug availability, heterogeneous populations, differences in local treatment protocols, and missing data due to asymptomatic patients who did not undergo SARS-CoV-2 testing, a strict comparison of patient outcomes between these studies is not possible.

Our multicenter study provides a long-term scenario regarding the morbidity, severity, and mortality of COVID-19 during the different phases of the pandemic in patients with CLL treated with venetoclax.

Because of the emerging higher risk of severe COVID-19 in patients affected by CLL treated with venetoclax in association with anti-CD20 antibody, we could suggest to better evaluate the addition of the monoclonal antibodies administration in the COVID-19 scenario.

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