LETTER TO THE EDITOR

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COVID-19 vaccination: Evaluation of risk for protection failure in chronic lymphocytic leukemia patients

To the Editor

Chronic lymphocytic leukemia (CLL) is one of the most frequent B cell malignancies and the most frequent leukemia in Western countries. The disease is clinically characterized by the accumulation of CD5 +/CD19+ B lymphocytes, which are diverted from their immuno-protection role, therefore resulting in an inherent risk for CLL patient to develop infections, such a predisposition being further potentiated as the result of chemo-immuno therapies (CIT).[1,2]

Although Italy was one of the countries most severely affected by the COVID-19 outbreak, the prevalence of symptomatic COVID-19 cases in CLL was overall in keeping with the advanced median age, and the known associated immunosuppression of CLL patients.[1,2] According to multicenter studies, however, higher rates of severe COVID-19 and of COVID-19-associated mortality were observed in these patients.[2]

In this context, CLL patients may represent an interesting model of immuno-compromised oncological elderly patients in which the efficacy of the novel vaccines against COVID-19 can be verified. The Italian vaccination program starting December 2020, although progressing slower than in other states, for example Israeli, United Kingdom, and United States, reached about 19% of vaccinated population of at the end of April 2021, when Israeli, United Kingdom, and United States had percentages of vaccinated population as high as 62%, 49%, and 40%, respectively.[3]

Therefore, as in similar studies carried out on US and Israeli CLL cohorts,[4,5] we have recently had the chance to investigate whether the COVID-19 vaccine is capable to trigger a specific antibody-mediated response in CLL by taking advantage of a well-characterized cohort of CLL patients from a single Italian institution reaching a complete two-dose vaccination at the end of April 2021.

The study included 46 CLL patients, diagnosed between 1993 and 2020, followed in a single institution (Hematology Unit of the University of Tor Vergata in Rome, Italy), who received two doses of the mRNA vaccine Comirnaty (BMT162b2 BioNTech/Pfizer GmbH). None of these patients had a documented history of SARS-CoV-2 infection. After providing informed consent for data collection, patients were tested for the development of antibodies against the SARS-CoV-2 S protein after a median of 26 days (interquartile range, IQR, 25–27) from the booster vaccination, without difference between patients scored negative (26 days, IQR

24–27) or positive (27 days, IQR 25–27) for antibody detection (see below).

Serum samples were evaluated by the chemo-luminescence Anti-SARS-CoV-2 immunoassay (Maglumi 2019-nCOV IgG) on the analyzer MAGLUMI™ 2000 Plus, a fully auto chemo-luminescence immunoassay analyzer for the quantitative detection of IgG class antibodies (Ab) against the SARS-CoV-2 S protein. This assay has a linear measurement range of 0.180–100 AU/ml, with a concentration <0.90 AU/ml considered as not reactive and ≥1.10 AU/ml considered as positive, with values between such cutoff being considered as ambiguous; no cases had values between 0.90 and 1.10 AU/ml in our series. When sample results exceeded the upper limit of the measuring range, samples were on-board diluted 1:10 or 1:20, following manufacturer's indications.

CLL patients were all characterized for sex, age, Rai staging, B2M serum levels, IgG levels, immunoglobulin-heavy-variable (IGHV) gene mutational status, NOTCH1 mutations, CD49d expression, and interphase fluorescence in situ hybridization for 17p13.1 (17p) deletion, 11q22.3 (11q) deletion, 13q14 deletion, and trisomy 12 by following standard methods, as previously reported.[6] Correlation between CLL features and positive/negative serology testing was estimated through unconditional logistic regression model.

Among CLL patients, 29/46 were males, and, at the time of vaccination, 20/46 patients had an age ≥ 70 years. Known CLL clinico-biological features found in their detrimental configuration at the time of vaccination included advanced (i.e., >0) Rai staging (35/46 cases), B2M > upper level of normal (24/46 cases), IgG < lower level of normal (26/46 cases), unmutated IGHV gene status (22/46 cases), presence of 17p and/or 11q deletions (16/46 cases), high CD49d expression (22/46 cases), and detection of NOTCH1 mutations (9/46 cases) (Figure 1).

Regarding therapies at the time of vaccination, 29/46 patients were on active treatment, whilst the remaining 17 patients were not treated (Figure 1), being either in the watch-and-wait CLL phase (7 cases), or off therapy (10 cases) from previous chemo-immunotherapy (CIT) or chemo-free regimens (median previous lines of therapy 1, range 1–2; median time from end of treatment to vaccination 28 months, IQR, 19–114 months). All treated patients were under chemo-free regimens with either ibrutinib (21 cases) or venetoclax (8 cases), both given as single agent. Among treated patients, 5 were treatment naïve (TN, all on ibrutinib), and 24 were

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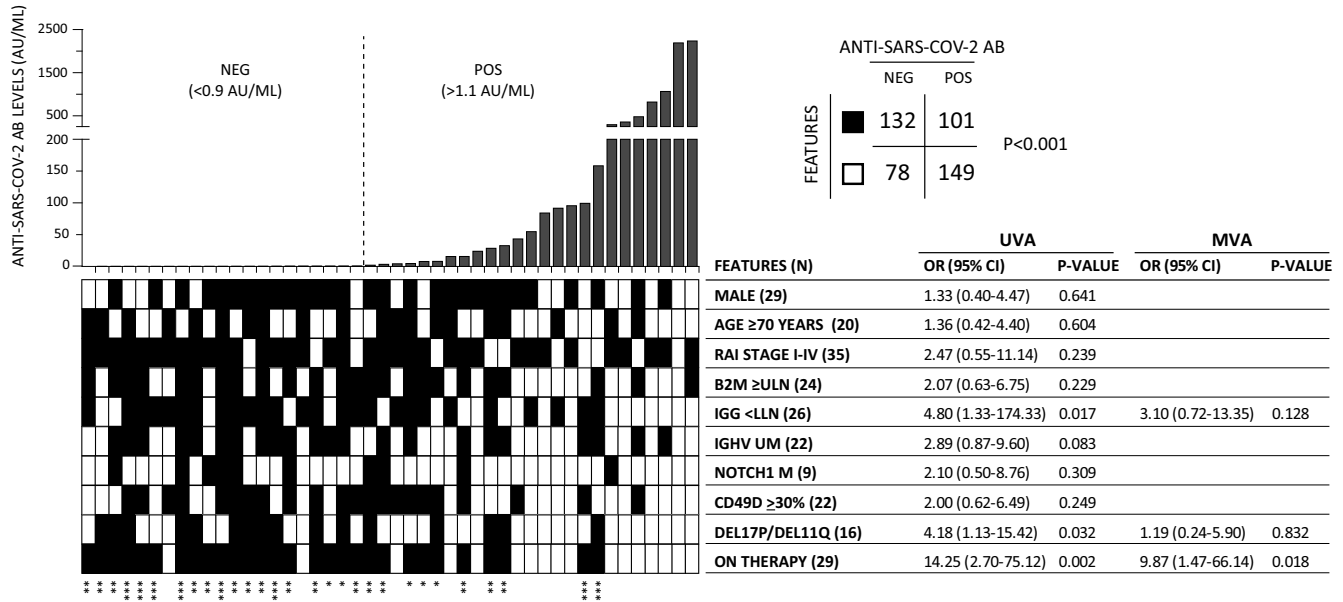
FIGURE 1 Anti-SARS-CoV-2 antibody response and correlation with clinico-biological chronic lymphocytic leukemia (CLL) features. Top left: Histogram plot of the individual antibody responses to vaccination in patients with CLL (n = 46). Each column represents the level of anti-SARS-CoV-2 antibodies (ab) in individual patients. The vertical dashed line splits cases with a negative (<0.9 AU/ml) serologic response versus positive (>1.1 AU/ml) serologic response, according to manufacturer's instructions. Bottom: the mutual relationship between serologic response and clinico-biological characteristics in CLL. Rows correspond to specific clinical and biological features and columns represent individual patients. Black and white boxes show the presence (black) or the absence (white) of the features reported on the right. On the right, univariable (UVA) and multivariable (MVA) analyses and corresponding odds ratio (OR) and 95% confidence interval (CI) for vaccination failure according to clinico-biological features; asterisks below the black and white heat map indicate patients on treatment with ibrutinib as first-line therapy (*), relapsed/refractory patients on treatment with ibrutinib (**), and relapsed/refractory patients on treatment with venetoclax (***), respectively. The χ2 test on the top right compares the serological results (negative vs. positive anti-SARS-CoV2 ab) with the presence (black box) or absence (white box) of negative clinico-biological features. del17p, 17p deletion; del11q, deletion 11q; LLN, lower limit of normal; M, mutated; ULN, upper limit of normal; UM, unmutated

refractory/relapsed (R/R) from previous CIT/chemo-free regimens (median previous lines of therapy 1, range 1–4). Thirty-one/46 patients had been treated with anti-CD20 monoclonal antibodies in previous regimens, including the 10 patients at present off therapy. None of these patients were on therapy with anti-CD20 monoclonal antibodies within a year from the start of vaccination.

Vaccine-induced Ab response was judged negative according to the established cut-off (<0.9 AU/ml of anti-SARS-CoV-2 S protein Ab) in 46% (21/46) of the patients (median value 0.18, range 0.10–0.77), a percentage in keeping with the previous reported observations.[4,5] The remaining 25 patients developed a sufficient specific Ab response (median value 54.71, range 1.96–2234.7).

As summarized in Figure 1, by separately considering the main patient-related (sex, age) and CLL-related features by univariable analysis, the male sex and all the other features in their worse configuration consistently associated with an increased risk of vaccination failure, that is, odds ratio (OR) > 1.0, such an increased risk turning out significant in the case of low IgG level (OR 4.80, 95% CI 1.33–174.33; p = 0.017), presence of 17p/11q deletions (OR 4.18, 95% CI 1.13–15.42; p = 0.032) and patients on treatment at the time of vaccination (OR 14.25, 95% CI 2.70–75.12; p = 0.002). Notably, in this context, the overall distribution of CLL-related features was significantly skewed toward their unfavorable configurations in CLL

cases unable to develop a sufficient Ab response upon vaccination (p < 0.001; Figure 1).

Finally, in a multivariable model that included the three significant features by univariable analysis, being on treatment at the time of vaccination emerged as the sole independent feature associated with an increased risk of vaccination failure for CLL patients (OR 9.87, 95% CI 1.47–166.14; Figure 1).

However, by only considering CLL patients on treatment at the time of vaccination, TN patients had a significantly lower risk (OR 5.0, 95% CI 0.49–50.83) than R/R cases (OR 18.21, 95% CI 3.27-101.52), and consistently higher Ab levels (median Ab levels TN: 4.61, range 0.61–7.97, vs. median Ab levels R/R: 0.45, range 0.10-158.3). On the other hand, within R/R patients, no difference was observed between cases on treatment with ibrutinib versus venetoclax both in terms of OR (ibrutinib: OR 16.50, 95% CI 2.69–101.33; venetoclax: OR 22.50, 95% CI 2.55–189.38), and median Ab levels (ibrutinib: 0.41, range 0.10–32.7; venetoclax: 0.14, range 0.10–158.3) (Figure 1).

Altogether, a low humoral response was documented in CLL patients undergoing COVID-19 vaccination, in keeping with the few recent studies on the topic.[5] The underlying reason(s) explaining this phenomenon may be ascribed to both therapy-related and disease-related factors. In our series, the majority of CLL patients on treatment (21/29) were receiving the BTK inhibitor ibrutinib, a drug that,

by blocking the B cell receptor pathway in both normal and malignant B cells, may significantly impair the humoral response to vaccination. In addition, however, a major impairment is observed in R/R patients as well as in patients bearing disease features characterizing a more aggressive clinical course, in keeping with similar observations recently made upon vaccination against pneumococcus, influenza, hepatitis B and herpes zoster viruses.[1,5]

Clinically, the impairment of antibody response to SARS-CoV-2 S protein vaccine in patients affected by CLL, especially if under treatment and/or in an advanced/more aggressive stage, strongly suggests to continue to apply to these patients caution measures, including recommendation for vaccination of relatives and close contacts, as well as the constant use of individual protection devices during social interactions. The application of serial serological testing to provide clinical and behavioral advices in CLL patients should be considered in the future.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Mauro FR, Giannarelli D, Galluzzo CM, et al. Response to the conjugate pneumococcal vaccine (PCV13) in patients with chronic lymphocytic leukemia (CLL). *Leukemia.* 2021;35(3).
2. Scarfò L, Chatzikonstantinou T, Rigolin GM, et al. COVID-19 severity and mortality in patients with chronic lymphocytic leukemia: a joint study by ERIC, the European Research Initiative on CLL, and CLL Campus. *Leukemia.* 2020;34(9):2354-2363.
3. Mathieu E, Ritchie H, Ortiz-Ospina E, et al. A global database of COVID-19 vaccinations. *Nat Hum Behav.* 2021;5(7):947-953.
4. Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. *Blood.* 2021;137(23):3165-3173.
5. Roeker LE, Knorr DA, Thompson MC, et al. COVID-19 vaccine efficacy in patients with chronic lymphocytic leukemia. *Leukemia.* 2021:1-3.
6. Tissino E, Pozzo F, Benedetti D, et al. CD49d promotes disease progression in chronic lymphocytic leukemia: new insights from CD49d bimodal expression. *Blood.* 2020;135(15):1244-1254.