RESEARCH LETTER

blood advances

TO THE EDITOR:

Antibody response to mRNA vaccination for COVID-19 in patients with AML receiving hypomethylating agents alone or with venetoclax

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Patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDSs) who are treated with hypomethylating agents (HMAs), alone or in combination with venetoclax, are an extremely vulnerable population due to advanced age, comorbidities, and treatment-induced neutropenia.[1,2] In addition, many of these patients receive HMA therapy in an outpatient setting, which continues until hematological disease progression.[1,2] All of these aspects make these patients very susceptible to breakthrough infection by SARS-CoV-2, especially given the emergence of new and highly contagious variants.[3-5] Because patients with blood cancer have been excluded from vaccine clinical trials, real-world data on vaccine immunogenicity are very important in this setting.[6] In particular, the assessment of antibody (Ab) levels may play a role in establishing a response to vaccination in this frail patient population. It is well known that the seroconversion rate after SARS-CoV-2 vaccination is particularly low in patients with hematological diseases with B-cell malignancies who are treated with monoclonal Ab–depleting B cells (eg, rituximab), as well as in those receiving Bruton tyrosine kinase inhibitors.[7-9] Some recent studies analyzed the anti-Spike Ab responses after SARS-CoV-2 vaccination in different hematologic malignancies and confirmed a low seroconversion rate in lymphoma and chronic lymphocytic leukemia; however, a good seroconversion rate was found after 2 vaccination doses in patients with chronic myeloid leukemia, multiple myeloma, acute lymphocytic leukemia, or AML.[9-11] However, there is no specific information on the humoral response after anti–SARS-CoV-2 vaccination (after the second and/or third vaccination doses) in patients with AML treated with HMAs.

We evaluated the Ab response to the mRNA vaccination (Pfizer-BioNTech vaccine) in 46 patients with AML (36/46) or high-risk MDS (10/46) undergoing therapy with HMAs alone or in combination with venetoclax (24/46 with HMA alone and 22/46 with HMA+venetoclax). The median age was 74 years (range, 42-85). All patients were undergoing active anticancer treatment for their hematologic disease and received the vaccination between April of 2021 and November of 2021. Data on demographic characteristics and Ab evaluation are summarized in Table 1. Only patients with AML received the combination of HMA and venetoclax. To assess Ab production, blood samples were collected after the second and/or the third dose of the Pfizer-BioNTech vaccine. The Ab test for SARS-CoV-2 immunoglobulin G (IgG) anti-Spike protein was performed using an automated electro-chemiluminescence immunoassay with a reactive (positive) level of anti-Spike IgG $\geq$0.8 U/mL. According to this cutoff value, patients who had an anti-Spike IgG Ab level $>$0.8 U/mL were classified as having a positive Ab response. In patients with a strong seroconversion (anti-Spike IgG level $>$2500 U/mL), it was not possible to define the exact Ab titer. All patients gave written consent for sample collection and Ab quantification.

At the time of data analysis, all 46 patients had received 2 doses of vaccine, and 24 of 46 patients (52%) had received a third dose. We performed the anti-Spike IgG assay in 33 of 46 patients (72%) after the second dose and in all 24 patients (100%) after the third dose. The Ab titer was assessed at a median of 4.3 months (range, 1-7.7) after the second vaccination and at a median of 1.5 months (range, 0.5-2.5) after the third vaccination. The Ab titers and the timing of the Ab assessment are shown in detail in Figure 1A and B, respectively. This study was approved by the Ethics Committee of the Friuli Venezia Giulia Region and was conducted according to the Declaration of Helsinki.

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Requests for data sharing may be submitted to Anna Candoni (anna.candoni@asufc.sanita.fvg.it).

Table 1. Patient characteristics and Ab assessment after the second and third vaccinations

	All cases	HMA alone	HMA+veneto	*P*
Patient characteristics				
No. of pts	46	24/46 (52)	22/46 (48)	
Age, median (range), y	74 (42-85)	73 (47-85)	75 (42-83)	ns
Hematologic cancer				
AML	36	14	22	
MDS High risk	10	10	0	
No. of HMA cycles at Vax (range)	2 (1-22)	2 (1-22)	2 (1-14)	ns
Ab test post-second Vax				
No. of pts who received 2 Vax	46/46 (100)	24/24 (100)	22/22 (100)	ns
No. of pts tested	33/46 (72)	17/24 (71)	16/22 (73)	ns
Time between Vax and Ab dosage, median (range), mo	4.3 (1-7.7)	4.5 (1-6.1)	4.2 (1-7.7)	ns
Pts with seroconversion*	30/33 (91)	16/17 (94)	14/16 (88)	ns
Ab level, U/mL				ns
1-100	14/33 (43)	8/17 (47)	6/16 (37.5)	
101-1000	11/33 (33)	7/17 (41)	4/16 (25)	
>1000	5/33 (15)	1/17 (6)	4/16 (25)	
Ab test post-third Vax				
No. of pts who received 3 Vax	24/46 (52)	14/24 (58)	10/22 (45)	ns
No. of pts tested	24/24 (100)	14/14 (100)	10/10 (100)	ns
Time between Vax and Ab dosage, median (range), mo	1.5 (0.5-2.5)	2 (0.5-2.5)	1.75 (0.5-2.5)	ns
Pts with seroconversion*	23/24 (96)	13/14 (93)	10/10 (100)	ns
Ab level, U/mL				ns
1-100	5/24 (21)	2/14 (14)	3/10 (30)	
101-1000	4/24 (17)	2/14 (14)	2/10 (20)	
>1000	14/24 (58)	9/14 (64)	5/10 (50)	

Unless otherwise noted, data are n (%) or n/N (%).
Ab, anti-Spike IgG Ab; ns, not significant; pts, patients; Vax, vaccination; veneto, venetoclax.
*Ab level >0.8 U/mL.

Seroconversion was documented in 91% (30/33) of cases after the second vaccination (mean Ab titer ± DS, 539 ± 840 U/mL; median, 101 U/mL; range, 8.5-2500) and in 96% (23/24) of cases after the third vaccination (mean Ab titer ± DS, 1620 ± 1116 U/mL; median, 2500 U/mL; range, 3.85-2500). No significant differences in seroconversion rates were observed after the second or third dose of vaccine between patients treated with HMAs alone and those treated with HMA+venetoclax (Table 1). Mean and median Ab titers were significantly higher after the third dose than after the second dose ($P = .003$, Student t test; $P = .0006$, Mann-Whitney U test), but there were no significant differences between the 2 cohorts. Interestingly, as shown in Figure 1C and D, only 15% (5/33) of patients had an Ab titer >1000 IU/mL after the second dose compared with 58% (14/24) after the third dose ($P = .0006$, χ^2 test). So far, no patient has developed COVID-19 infection after vaccination.

The important limitations of this analysis are the lack of data regarding cell-mediated immunity and Ab quantification at different time points after vaccination. In addition, we do not know how important the humoral response is in this infection and whether there is a relationship between anti-Spike IgG levels and the degree of protection against SARS-CoV-2 infection (the so-called "preventive Ab titer"); this study is inadequate to define this threshold. Despite these limitations, this is the first report on the humoral response after RNA vaccination (Pfizer-BioNTech vaccine) in elderly patients with AML/MDS who are undergoing treatment with HMAs, with or without venetoclax. These preliminary data show that, in patients with AML or MDS who are treated with HMAs, with or without venetoclax, the seroconversion rate is already favorable after the first 2 doses of SARS-CoV-2 vaccine (seroconversion in 91% of the analyzed population). However, it should be emphasized that a significant proportion of our patients experienced an attenuated seroconversion after the first 2 doses. Indeed, 43% (14/33) of the Ab-positive cases had an anti-Spike titer <100 U/mL after the second dose of vaccine. As reported in Table 1 and Figure 1D, the Ab titers appear to increase significantly after the third vaccination dose, with no difference between patients treated with HMAs alone and those treated with HMA+venetoclax. These favorable results should be confirmed by further prospective studies involving more patients over an extended follow-up period; however, they highlight the great importance of the third vaccination dose in enhancing the humoral response in this vulnerable population.

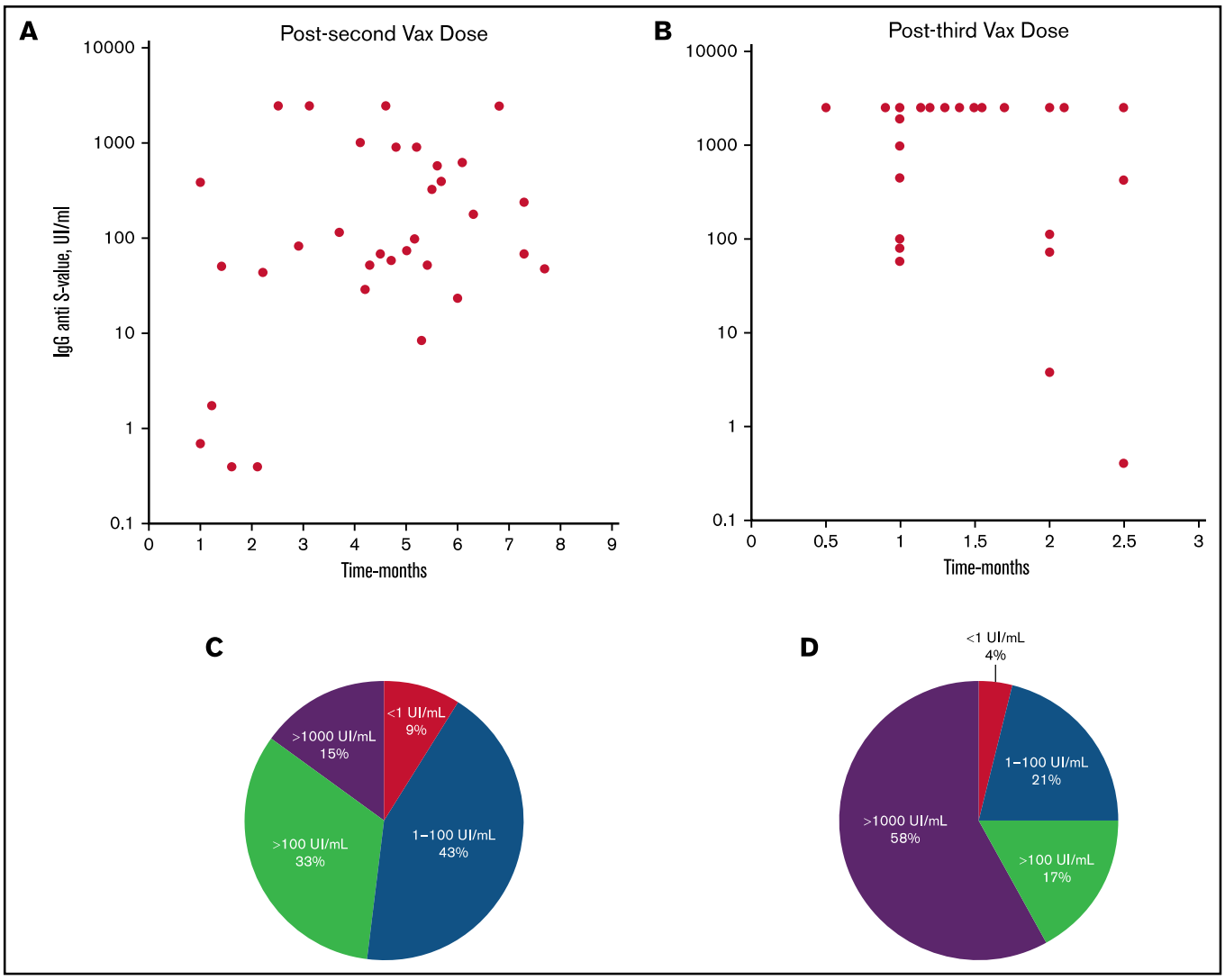

Figure 1. Distribution of Ab titers after vaccinations. Distribution of Ab titers after the second (A) and third (B) doses of vaccine (Vax). Ab titers were significantly higher after the third dose of vaccine than after the second dose (mean ± DS, 1620 ± 1116 U/mL vs 539 ± 840 U/mL; $P = .003$). Percentages of patients with different Ab levels after the second (C) and third (D) vaccinations. Only 15% (5/33) of patients had Ab titers >1000 U/mL after the second dose (C) compared with 58% (14/24) after the third dose (D) ($P = .0006$). S, Spike.

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