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LETTERS TO THE EDITOR

Effects of active cancer treatment on safety and immunogenicity of COVID-19 mRNA-BNT162b2 vaccine: preliminary results from the prospective observational Vax-On study

National health plans prioritized cancer patients on active treatment for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination because of high morbidity and mortality rates associated with coronavirus disease-19 (COVID-19).[1] The messenger RNA (mRNA) vaccine approval studies excluded recipients of immunosuppressive therapy,[2,3] raising concerns among the oncology community. Herein, we assessed the effects of active treatments on safety and immunogenicity of SARS-CoV-2 mRNA-BNT162b2 vaccine in patients with solid malignancies.

This cohort study prospectively enrolled patients who started the 3-week apart mRNA-BNT162b2 vaccine schedule from 9 March to 12 April 2021 (timepoint-1). Those on active treatment within the previous 28 days accounted for the exposed cohort (ExC). Patients who had discontinued such treatment by at least 28 days represented the control cohort (CC). Safety analysis and quantification of anti-SARS-CoV-2 spike immunoglobulin G (IgG) were carried out before the second dose (timepoint-2) and 8 weeks thereafter (timepoint-3). The titration was carried out using the Abbott (Abbott Laboratories, Diagnostics Division, Sligo, Ireland) SARS-CoV-2 chemiluminescent microparticle immunoassay and seroconversion was defined at $\geq$50 AU/ml IgG titer. No SARS-CoV-2 real-time RT-PCR swab test or serologic titer was required at baseline. The study was approved by referring ethics committee (Protocol N.595/CE Lazio1) and formally registered (EudraCT N.2021-002611-54).

Cohorts were compared using appropriate tests for categorical and continuous variables. A multivariable logistic regression model was implemented to determine clinical factors associated with the risk of adverse events. Univariate and multivariate analysis, including predefined clinical variables, was carried out by fitting a generalized linear model on seroconversion response and log IgG titer (Supplementary Statistical Analysis, available at https://doi.org/10.1016/j.annonc.2021.09.009).

We enrolled 366 patients (81 in the CC and 285 in the ExC) and the cohorts were mostly homogeneous (Supplementary Figure S1 and Table S1, available at https://doi.org/10.1016/j.annonc.2021.09.009). The adjuvant chemotherapy setting, prevalent in CC, accounts for the difference. Severe adverse events were rare (1%). The most common adverse reactions were mild injection site reactions. Systemic adverse events did not exceed 17% of cases (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2021.09.009) and were significantly associated with specific features [i.e. female sex, Eastern Cooperative Oncology Group performance status 2 (ECOG PS2), or granulocyte colony-stimulating factor (G-CSF) use, Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2021.09.009]. At timepoint-2, the median IgG titer {131 AU/ml [95% confidence interval (CI) 77-173] versus 62 AU/ml (95% CI 42-82), $P = 0.029$}, median log IgG titer ($P = 0.033$; Figure 1A), and seroconversion rate (65% versus 52%, $P = 0.048$; Figure 1B) were significantly higher for CC. The median IgG titer [CC 2256 AU/ml (95% CI 1471-3491) versus ExC 1530 AU/ml (95% CI 1099-2072), $P = 0.29$], median log IgG titer ($P = 0.47$), and percentage of seroconverted patients (CC 89% versus ExC 91.2%, $P = 0.56$) did not differ at timepoint-3. A significant 15-fold or greater increase in median IgG titers and seroconversion rates up to 91% were observed from timepoint-2 to -3 within the same cohorts ($P < 0.001$). Multivariate analysis did not confirm a negative interaction between cytotoxic chemotherapy and antibody response, but ECOG PS2 and G-CSF use were significantly associated with lower IgG titer and lack of seroconversion after either dose of vaccine (Supplementary Tables S4 and S5, available at https://doi.org/10.1016/j.annonc.2021.09.009).

In conclusion, we confirmed in a large population a favorable safety profile of mRNA-BNT162b2 vaccine, which may reassure on maintaining active cancer treatment throughout the whole vaccination schedule.[4] Patients with specific conditions, such as female sex and G-CSF usage, should be cautioned about increased risk of side effects. Humoral response to first dose is confirmed as inadequate.[5] Booster vaccine dose resulted in an exponential increase in IgG titer and high rate of seroconversion, arguing against delays in dosing schedule. Although some clinical features predict reduced immunogenicity, further experimental testing is required to confirm their significance.

F. Nelli[1]*, A. Fabbri[1], A. Onorato[1], D. Giannarelli[2], M. A. Silvestri[3], J. R. Giron Berrios[1], A. Virtuoso[1], E. Marrucci[1], C. Signorelli[1], M. G. Chilelli[1], F. Primi[1], M. Schirripa[1], M. Mazzotta[1] & E. M. Ruggeri[1]

[1]Department of Oncology and Hematology, Medical Oncology Unit, Central Hospital of Belcolle, Viterbo; [2]Clinical Trial Center, Biostatistics and Bioinformatics Unit, Scientific Direction, IRCCS Regina Elena National Cancer Institute, Rome; [3]Department of Oncology and Hematology, Microbiology and Virology Unit, Central Hospital of Belcolle, Viterbo, Italy.
(*E-mail: fabrizio.nelli@asl.vt.it).

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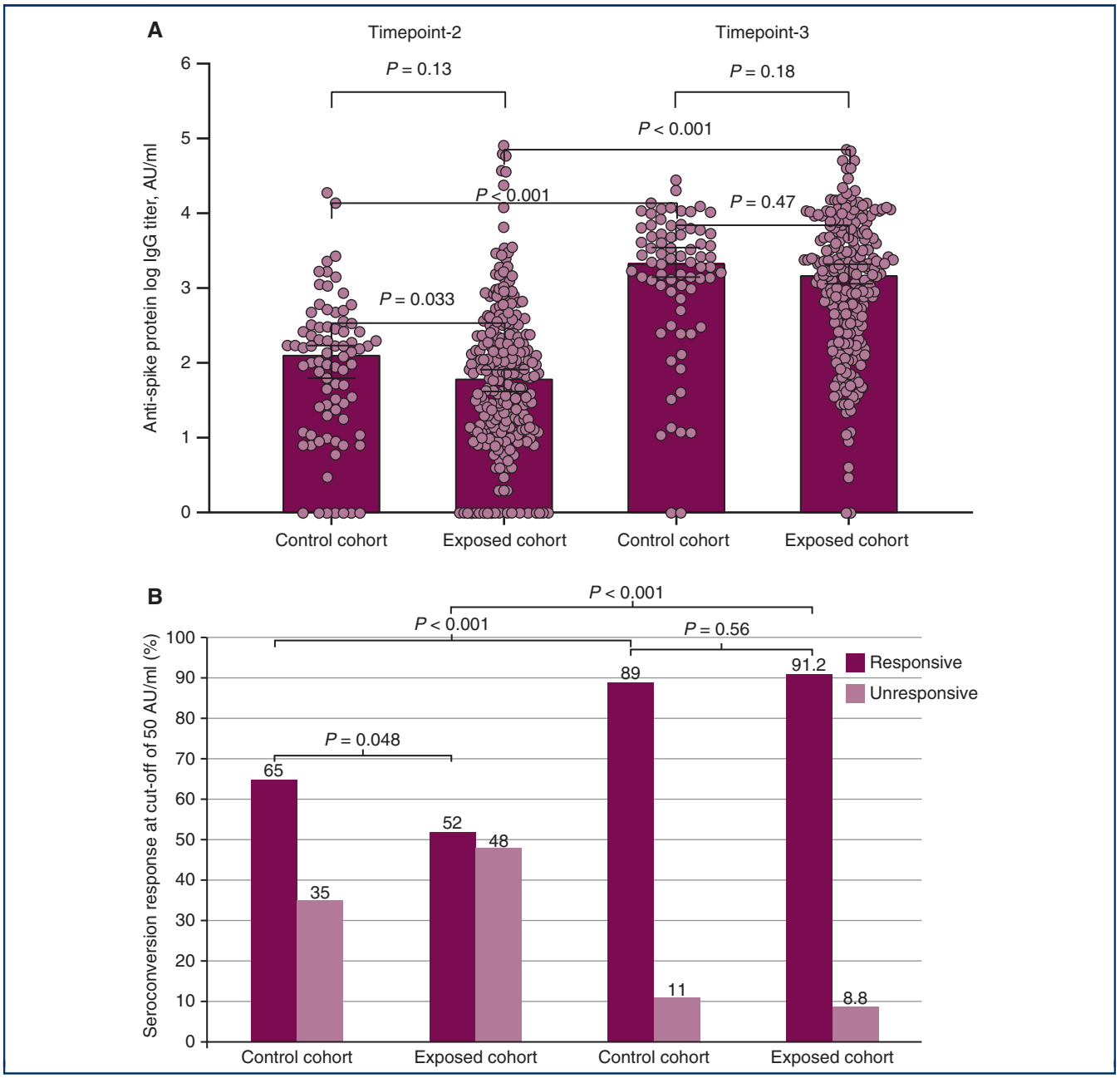

Figure 1. Antibody and seroconversion responses after either dose of mRNA-BNT162b2 vaccine.
(A) Comparison of distributions and medians of anti-SARS-CoV-2 spike protein IgG titers (logarithmic values). Bars represent median values with 95% confidence interval. (B) Comparison of seroconversion response rates at a cut-off of 50 AU/ml. Control cohort, patients with discontinuation of active treatment by at least 28 days; exposed cohort, patients on active treatment within previous 28 days; timepoint-1, assessment before second mRNA-BNT162b2 vaccine dose; timepoint-3, assessment at 8 weeks after second vaccine dose.

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