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European Journal of Cancer 176 (2022) 164–167

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Letter to the Editor

Duration of humoral response to the third dose of BNT162b2 vaccine in patients with solid cancer: Is fourth dose urgently needed?

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Received 4 September 2022; accepted 6 September 2022
Available online ■ ■ ■

We had previously reported on the immunogenicity of the BNT162b2 mRNA COVID-19 vaccine (Tozinameran) in a large cohort of patients with cancer after the first and the second doses [1], and we subsequently showed the rapid decline of humoral response over the time until 6 months of follow-up [2,3]. We have also recently reported on the potentiation of humoral response after the third dose in this frail population [4], in line with other studies [5–9].

Herein, we assess the long-term (at 4 months) serological response to the third dose in patients with solid cancer under active treatment.

Patients with solid cancer who received the third dose at our Institute were included in the study. Written informed consent was obtained by all the participants before any study procedures. The study protocol was reviewed and approved by the local Ethical Committee (Prot. protocol RS1463/21). All patients received the additional dose of Tozinameran at least 28-days after the primary 2-doses cycle of vaccination. Anti-Spike (S) immunoglobulin G (IgG) titre was evaluated using the Liason® chemiluminescent-immunoassay (Diasorin, Saluggia, Italy) post-third dose at 16 weeks after the inoculation, as at post-second vaccination. A cut-off of 15 AU/ml of IgG was adopted to define the response and serological positive status. Antibody levels were compared using Kruskal–Wallis rank sum test. Correlation of Geometric Mean Concentration (GMC) of IgG titre and clinical characteristics (sex, age, ECOG PS, BMI, Comorbidities, chronic steroid use, number of metastatic sites, setting of therapy, type of metastasis and type of anticancer treatment) was analysed by using a multiple linear regression model.

DOI of original article: https://doi.org/10.1016/j.ejca.2022.01.011.
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https://doi.org/10.1016/j.ejca.2022.09.006

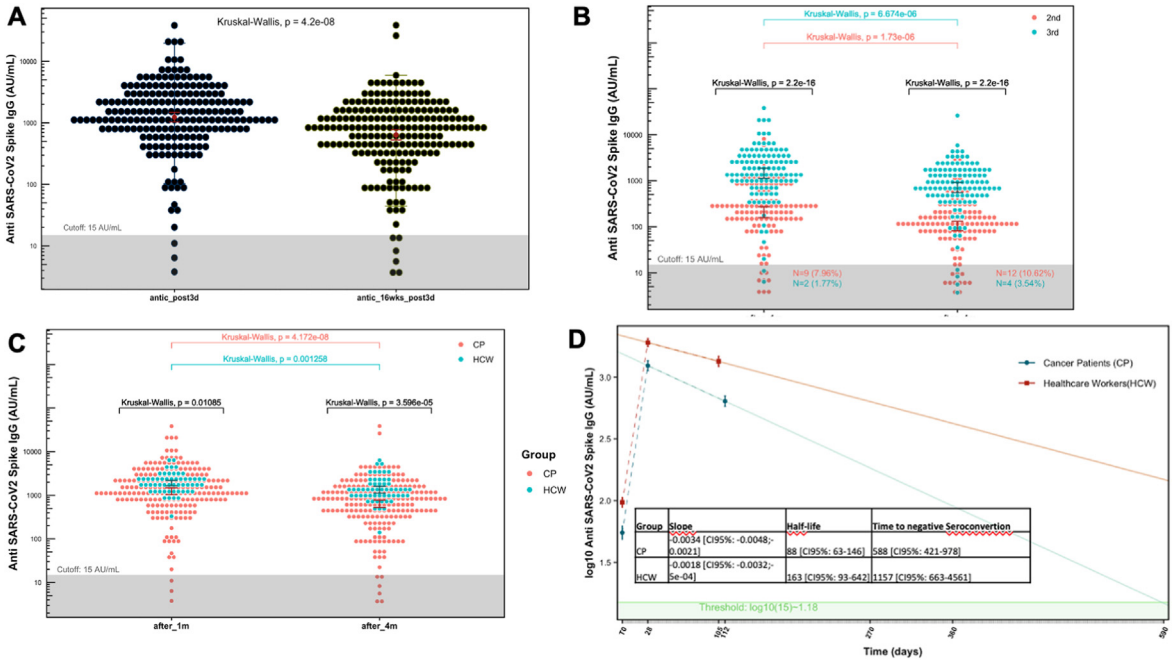

Fig. 1. **(A) Dot plots of anti-S IgG titre assessed at 1 and 4 month after the third dose (B) Dot plots of anti-S IgG after the second (pink colour) and third dose (light blue colour) in patients with cancer (C) Dot plots of anti-S IgG a 1 and 4 months after the third dose in patients with cancer (pink colour) and in healthcare workers (light blue colour)**. A logarithm scale was used for IgG titre. The grey area is the area below the pre-fixed cut-off of positivity. Inside each dot plot, the geometric mean concentrations ± standard errors were represented by a black point with error bars; the median is depicted as a red asterisk. ∗All comparisons were statistically significant. **(D) Linear regression analysis of IgG titre (y-axis) by group over-the time (x-axis)**.The IgG titre was reported using logarithmic scale. The means of IgG titre observed at different timepoints were reported as dots (rounded light blue for CP and square red dots for HCW) with error bars. Parameters (slope, half-life and time to negative seroconvertion) of linear regression model were reported in the table on the left inferior corner. Green horizontal line represents the threshold of positivity of IgG titre (15 AU/ml). The intersection of the linear regression line of each study group with the green line represents the estimated time to negative seroconvertion. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article).

A cohort of healthcare workers receiving the booster dose was also evaluated and compared with patients cohort using appropriate tests. A linear regression model was used for the estimation of half-lives of IgG and the calculation of the time of 'negative seroconvertion' (time needed to reach a value < 15 AU/ml).

We evaluated 216 patients at 4-months after the third dose. The median age was 67 (range 24–88) years. Breast cancer (28.2%) and lung cancer (23.4%) were the most common tumour subtypes.

Most of patients (200/216, 92.6%) were on active anticancer treatment during the 28-days before the administration. Chemotherapy alone or in combination with monoclonal antibodies (anti-HER2 and antiangiogenic drugs, immune-checkpoint inhibitors) was the most used treatment (33%), followed by anti-CTLA4 and anti PD-(L)-1 checkpoint inhibitors (23%) and targeted therapy (21%). A chronic steroid use (daily assumption started at least 30 days before the vaccination) was reported in 23 (10.7%) patients.

The proportion of patients with a positive serological status was 97.7% (211/216) similar to that observed (98.8%, 402/407) in the post-1 month analysis, previously reported [4]. The GMC at 4-months was 653.61 AU/ml, lower than the value previously assessed at 1-month after the booster (1054.5 AU/ml).

Considering patients evaluated at 1 and 4 months after the third dose (no = 207), GMC significantly decreased of 1.93 fold from 1239.63 to 639.42 AU/ml and seronegative subjects doubled, although they continued to represent a very limited subset (1.4 and 2.8% at 1 and 4-months, respectively) (Fig. 1A).

Among the clinical characteristics analysed, only female sex and chronic steroid use were significantly associated with lower IgG titre (Table S1, Fig S1). The type of anticancer treatment did not significantly affect the antibody level at 4 months (Fig S2).

A comparable decay of IgG titre at 1 and 4 months after the second and third dose (fold of change = 1.99 vs 2.02, respectively) was found in the subset of evaluable patients (no = 113), although the absolute levels of IgG after the booster were 7-fold higher than post-second dose. Moreover, seronegative patients at 4 months from vaccination decreased at 3.54% with the third dose compared to 10.62% with the second dose (Fig. 1B).

All healthcare workers cohort had a positive serological status post 1 (no = 100) and 4-months (no = 79)

from the booster. The IgG titre was significantly lower in patients with cancer than in healthcare workers both at 1 (1239.63 versus 1904.80 AU/ml, $p < 0.001$) and 4 months (639.42 versus 1342.84 AU/ml, $p < 0.001$) after the third dose. The decrease of IgG titre between 1 and 4 months after the third dose was of 1.94 fold in patients and 1.42 in healthcare workers (Fig. 1C).

The half-life of serum IgG was estimated to be lower in patients (88 days) than in healthcare workers (163 days). The estimated time from positive to negative serological status (<15AU/ml) was 588 and 1157 days for patients and healthcare workers, respectively (Fig. 1D). Clinical factors did not significantly influence the IgG half-life in patients with cancer. However, shortest IgG half-lives were observed among patients receiving chemotherapy, under chronic steroid therapy, with metastatic disease and high disease burden (>3 sites of metastases) (Table S2).

In this cohort study, we observed a decay of humoural response to the third dose in patients with cancer after a follow-up time of 4 months, which was similar to that observed after the second dose, although higher absolute level of IgG in addition to limited number of seronegative subjects were reached with the booster. More rapid decline of humoral response was observed in patients than in the healthcare workers, as evidenced by the shorter IgG half-time (2.4 versus 5.4 months) and the estimated time from positive to negative serological status (19.6 versus 38.5 months).

Our data showing the decline of humoural response at 4-months after third dose in patients with cancer support the early administration of a fourth vaccination in this frail population, as recommended in several countries. Of note, some patients with certain clinical characteristics (i.e. receiving chemotherapy or chronic therapy with steroids) should be considered with higher priority for a further vaccination or more closely monitored due to their weaker humoral response [10].

As limitations of this study, we evaluated only the anti-S IgG level and not also the neutralising antibodies, even if their level were often correlated. Moreover, T-cell immunity and the infection rate of study population have not been assessed. Further prospective studies are warranted to establish the indications and the timing of the second booster dose especially in patients with cancer.

Funding

None.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: V.D.N. received speakers' fee by Astrazeneca, MSD, BMS, Istituto Gentili, Boehringer Ingelheim. V.D.N. received grant consultancies by Astrazeneca, MSD, BMS, Boehringer Ingelheim and travels' fee from MSD and Boehringer Ingelheim. V.D.N. received institutional research grants from Roche. F.C. member of advisory board of GSK, Roche, Astra Azeneca, Eli-Lilly. FC received speakers' fee by GSK, Roche, Astra Azeneca, Eli-Lilly, Novartis, Amgen, Pfizer, MSD, BMS, Astellas, Eli-Lilly. All remaining authors have declared no conflicts of interest.

Acknowledgements

The authors thank medical oncologists (Paolo Carlini, Gianluigi Ferretti, Maria Bassanelli Fabiana Letizia Cecere, Elvira Colella, Consuelo D'Ambrosio, Emanuela Dell'Aquila, Loretta D'Onofrio, Virginia Ferraresi, Alberto Fulvi, Simona Gasparro, Paola Malaguti, Elisa Onesti, Domenicangela Pellegrini, Michelangelo Russillo, Antonella Savarese, Sabrina Vari, Massimo Zeuli), residents (Antonella Cosimati, Vittoria Barberi, Mattia Di Civita, Federica Riva, Maria Teresa Maccallini, Gariazzo Ludovica), nurses of Medical Oncology 1 Unit, hospital pharmacists, medical direction members and data managers (Elisabetta Bozzoli, Alessandra Zambardi, Viviana Cangiano, Barbara Conforti) of IRCCS Regina Elena National Cancer Institute in Rome, Italy for their commitment to the COVID-19 vaccination campaign for patients with cancer. The authors thank the patients afferent to our Unit and their families.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.09.006.

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