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Efficacy of mRNA anti-SARS-CoV-2 vaccination and dynamics of humoral immune response in patients with solid tumors: results from the institutional registry of an Italian tertiary cancer center

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Abstract

Background: Systemic immunosuppression characterizing cancer patients represents a concern regarding the efficacy of anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination, and real-world evidence is needed to define the efficacy and the dynamics of humoral immune response to mRNA-based anti-SARS-CoV-2 vaccines.

Methods: We conducted an observational study that included patients with solid tumors who were candidates for mRNA anti-SARS-CoV-2 vaccination at the Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy. The primary objective was to monitor the immunologic response to the mRNA anti-SARS-CoV-2 vaccination in terms of anti-spike antibody levels. All the patients received two doses of the mRNA-1273 vaccine or the BNT162b2 vaccine. Healthcare workers served as a control group of healthy subjects.

Results: Among the 243 patients included in the present analysis, 208 (85.60%) and 238 (97.94%) resulted seroconverted after the first and the second dose of vaccine, respectively. Only five patients (2.06%) had a negative titer after the second dose. No significant differences in the rate of seroconversion after two vaccine doses were observed in patients as compared with the control group of healthy subjects. Age and anticancer treatment class had an independent impact on the antibody titer after the second dose of vaccination. In a subgroup of 171 patients with available data about the third timepoint, patients receiving immunotherapy with immune checkpoint inhibitors seem to have a higher peak of antibodies soon after the second dose (3 weeks after), but a more pronounced decrease at a late timepoint (3 months after).

Conclusions: The systemic immunosuppression characterizing cancer patients did not seem to dramatically affect the humoral response to anti-SARS-CoV-2 mRNA vaccines in our population of patients with solid tumors. Further investigation is needed to dissect the interplay between immunotherapy and longitudinal dynamics of humoral response to mRNA vaccines, as well as to analyze the cellular response to mRNA vaccines in cancer patients.

Keywords: cancer patients, COVID19, mRNA vaccine, SARS-CoV-2, solid tumors, vaccination

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Introduction

The emergence in December 2019 of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulted in devastating consequences on global health. Fortunately, the rapid and widespread adoption of anti-SARS-CoV-2 vaccination based on mRNA platforms has dramatically reduced the morbidity and mortality associated with the SARS-CoV-2-related coronavirus disease 2019 (COVID-19).[1–4]

Cancer patients represent a particularly vulnerable population to the adverse clinical outcomes of COVID-19, given the immunosuppressive status linked to the malignancy itself and to specific anticancer treatments (e.g. cytotoxic and myelotoxic agents). Indeed, a multicenter study performed in China at the beginning of SARS-CoV-2 spread showed that COVID-19 patients with cancer had a higher risk of severe outcomes,[5] even if another large cohort study suggested that mortality from SARS-CoV-2 infection in cancer patients appears to be mainly driven by age and comorbidities,[6] similar to the general population. Thus, international organizations, such as the European Society for Medical Oncology, have released statements and guidelines to address the issues and concerns on immunizing patients with solid and hematological malignancies, recommending that cancer patients should be vaccinated against SARS-CoV-2 regardless of any other indications (i.e. age) and positioned at high prioritization.[7] However, the systemic immunosuppression characterizing cancer patients represents a concern also regarding the efficacy of anti-SARS-CoV-2 vaccination. Recently, several reports have started to clarify the spectrum of anti-SARS-CoV-2 vaccine response among cancer patients in a real-world setting. Still, the follow-up time of most studies is limited.[8] Considering the underrepresentation of cancer patients in anti-SARS-CoV-2 vaccine trials, further evidence is needed to define the efficacy and the dynamics of the humoral immune response to mRNA-based anti-SARS-CoV-2 vaccines. Moreover, a precise dissection of the dynamics and determinants of the humoral immune response to anti-SARS-CoV-2 mRNA vaccines in cancer patients may be of particular interest since it may help to speed up the development of mRNA-based anticancer treatments, one of the most promising biotechnologies of the next-generation cancer immunotherapy.[9] Starting from these considerations, in the present study, we report on the data of a large institutional registry aimed at assessing and monitoring the immunologic response to mRNA anti-SARS-CoV-2 vaccination in patients with solid tumors.

Methods

Study design and patients' population

This was an observational study that included patients with solid tumors who were candidates for mRNA anti-SARS-CoV-2 vaccination at the Fondazione IRCCS Istituto Nazionale dei Tumori of Milan between 1 April and 30 April 2021 according to the national guidelines and international recommendations. All the patients included in the present study had received two doses of the mRNA-1273 vaccine or the BNT162b2 vaccine at the time of the data cutoff (1 November 2021). The second dose of the mRNA-1273 and BNT162b2 vaccines was administered 24–31 days after the first dose according to the local and national guidelines. No heterologous vaccination was allowed.

As per protocol, healthcare workers at the same institution served as a control group to assess the immunogenicity after two doses of mRNA vaccine (about 35 days after the second dose) in a population of healthy subjects.

The primary objective of the study was to monitor the immunologic response to the mRNA anti-SARS-CoV-2 vaccination in terms of anti-spike antibody levels in patients with solid tumors. Secondary objectives included the following: (a) the comparison of the immunologic response to the mRNA anti-SARS-CoV-2 vaccination in terms of anti-spike antibody levels between cancer patients and a control population of healthy subjects and (b) the evaluation of the role of clinicopathological characteristics, anticancer treatment class, and different mRNA anti-SARS-CoV-2 vaccines received in the seroconversion dynamics after vaccination. The main inclusion criteria were as follows: (a) cytologically or histologically confirmed diagnosis of a solid malignancy; (b) age $\geq$ 18 years; and (c) willingness to undergo mRNA anti-SARS-CoV-2 vaccination according to the national guidelines and international recommendations. The main exclusion criteria were as follows: (a) allergy to any vaccine component; (b) previous severe reactions after non-anti-SARS-CoV-2 vaccinations conditioning the exclusion from anti-SARS-CoV-2 vaccination programs; and (c) pregnancy or breast-feeding for female patients. For the present report, we

excluded patients with prior known SARS-CoV-2 infection. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the Fondazione IRCCS Istituto Nazionale dei Tumori of Milan (INT 119/21). All the patients and healthcare workers signed an informed consent form.

Evaluation of anti-SARS-CoV-2-spike antibody serum levels

Anti-SARS-CoV-2-spike antibody serum levels were evaluated at the following timepoints: (1) after the administration of the first dose and prior to the administration of the second dose, T1; (2) from 2 to 6 weeks after the administration of the second vaccine dose, T2; and (3) about 3 months after the administration of the second vaccine dose, T3. A T0 timepoint, prior to the administration of the first dose, was analyzed to exclude the suspected previous infections of SARS-CoV-2. The Roche Elecsys® Anti-SARS-CoV-2 S (Roche S tAb, Roche Diagnostics International Ltd, Rotkreuz, Switzerland) was used to quantitatively measure the level of antibodies to the receptor-binding domain of the spike (S) protein of the SARS-CoV-2 according to the manufacturer's instructions. The anti-SARS-CoV-2 S antibodies concentration was expressed in units per milliliter (U/mL). A concentration <0.80 U/mL was interpreted as negative for the presence of anti-SARS-CoV-2 S antibodies, whereas a concentration $\geqslant 0.80$ U/mL was interpreted as positive.[10]

Statistical analyses

Continuous variables were reported as median and range or interquartile range (IQR) and categorical variables as proportions. Associations between categorical variables were tested by the Chi-square statistic or Fisher's exact test whenever appropriate. For each patient, the percentage change in the anti-SARS-CoV-2 antibody titer with respect to $T_{(i-1)}$ (with $i = 2, 3$; i.e. 100*[T2 or T3 value] − [T1 or T2]/[T1 or T2]) was computed and a graphical representation of the median values according to the variables of interest was performed. Due to the highly positive skewed distributions of the data, the subsequent analysis was conducted on the log-transformation IgG data.

To investigate the effects of all the available clinicopathological characteristics, anticancer treatment class and different mRNA anti-SARS-CoV-2 vaccines received on the anti-spike antibody levels at T2, a one-way analysis of variance (ANOVA) was carried out. Anticancer treatments were classified as follows: biological therapy (including monoclonal antibodies other than immune checkpoint inhibitors, antibody–drug conjugates, tyrosine kinase inhibitors and other small molecules, hormone therapy, mTOR inhibitors), chemotherapy, immunotherapy, chemotherapy + immunotherapy, biological therapy + immunotherapy, radiotherapy/chemotherapy + radiotherapy. A multivariate initial model including all of the variables that were statistically significant at univariate analysis was implemented. A more parsimonious final model was then obtained using a backward selection procedure that retained only those variables reaching the conventional level of significance of 5%. The same approach was applied using the difference between the anti-spike antibody levels at T2 and T3 on their logarithmic scale (Δ_{T3-T2}).

The time trends profiles of the anti-spike antibody levels were assessed by resorting to mixed models and by considering antibody levels (on a logarithmic scale) as a function of time (fixed factor, T1, T2, and T3) and subjects (random factor). In addition, the time trends were studied even by considering the following covariates: sex, age (dichotomized at 50 years), and class of anticancer treatment and their possible interactions with the time factor. The most appropriate matrix of variance–covariance for each model was selected according to the Akaike Information Criterion.

All statistical analyses were performed with SAS software (Version 9.4.; SAS Institute, Inc., Cary, NC, USA), adopting a nominal significance level of $\alpha = 0.05$.

Results

Patients' characteristics

Among the 325 patients with solid tumors included in the registry, 243 matched the following criteria: (i) having received the two doses of mRNA anti-SARS-CoV-2 vaccine, (ii) no previous SARS-CoV-2 infection, and (iii) having a non-missing value for the anti-spike antibody level at both T1 and T2 (Supplemental Figure 1). The subjects' clinical and pathological characteristics, anticancer treatment class, and different mRNA anti-SARS-CoV-2 vaccines received are shown in

Table 1. Patients' characteristics.

Variable	Patients in the analysis ($n=243$)	
	N	**%**
Age		
Median (range)	62 (24–84)	
Sex		
Male	100	41.15
Female	143	58.85
Stage of tumor		
Metastatic	173	71.19
Localized	70	28.81
Type of tumor		
Lung	41	16.87
Breast	51	20.99
Gynecologic	20	8.23
Melanoma	40	16.46
NET	9	3.7
Sarcoma	18	7.41
Gastrointestinal	17	7
Head and neck	11	4.53
Genitourinary	24	9.88
Other	12	4.94
Treatment		
Biological therapy	106	43.62
Chemotherapy	62	25.51
Chemotherapy + immunotherapy	9	3.7
RT/chemo + RT	2	0.82
Immunotherapy	34	13.99
Biological therapy + immunotherapy	5	2.06
None	15	6.17
–	10	4.12
Type of vaccine		
mRNA-1273	126	51.85
BNT162b2	117	48.15

NET, neuroendocrine tumor; RT, radiotherapy.

Table 1. Details about specific anticancer treatments are reported in Supplemental Table 1. In particular, patients receiving immunotherapy or chemo-immunotherapy were all treated with anti-programmed cell 1/programmed cell death ligand 1 antibodies as the immunotherapeutic agents (Supplemental Table 1). The percentages of patients receiving the mRNA-1273 vaccine and the BNT162b2 vaccine were similar. The median age of patients was 62 years (range: 24–84), almost 60% of the patients were women and more than 70% had a metastatic tumor. The most frequent tumor types were breast and lung cancers followed by melanoma (20.99%, 16.87%, and 16.46%, respectively). The majority of patients were receiving a biological anticancer therapy at the time of the first dose of vaccine, and about 6% of patients were not under active anticancer treatment.

Dynamics of seroconversion in patients with solid tumors

Among the 243 patients included in the present analysis, 208 (85.60%) and 238 (97.94%) resulted seroconverted at T1 and T2, respectively; only five patients (2.06%) had a negative titer after the second dose of vaccine. The median value of the anti-spike antibody titer was equal to 15.4 U/mL (IQR: 2.45–52.6) at T1 and 1422.0 U/mL (IQR: 555.0–4066.0) at T2.

To compare the immunological response to the mRNA anti-SARS-CoV-2 vaccination in terms of anti-spike antibody levels at T2 between cancer patients and the control population of healthy subjects, we performed a sex- and age-matched analysis, comparing the response rate and the antibody titer in 164 patients and in 164 healthy workers (96 females, median age 56.5 years, range: 47–62 in both case and control). No significant differences were observed in the rate of seroconversion after the second dose of vaccination in our population of patients with solid tumors compared with the control group of healthy workers. In the control group, the seroconversion rate after the second dose of vaccine was 99.4% (95% confidence interval [CI]: 96.7–100%) compared with a 98.8% rate (95% CI: 95.7–99.9%) in the patients' group ($p=0.5619$). The median level of anti-spike antibody at T2 was equal to 1812.5 U/mL (IQR: 721.0–4456.5) in the patients' group compared with 1129.5 U/mL (IQR: 667.5–1840.5) in the control group ($p=0.6594$ adjusted for the dose administration time).

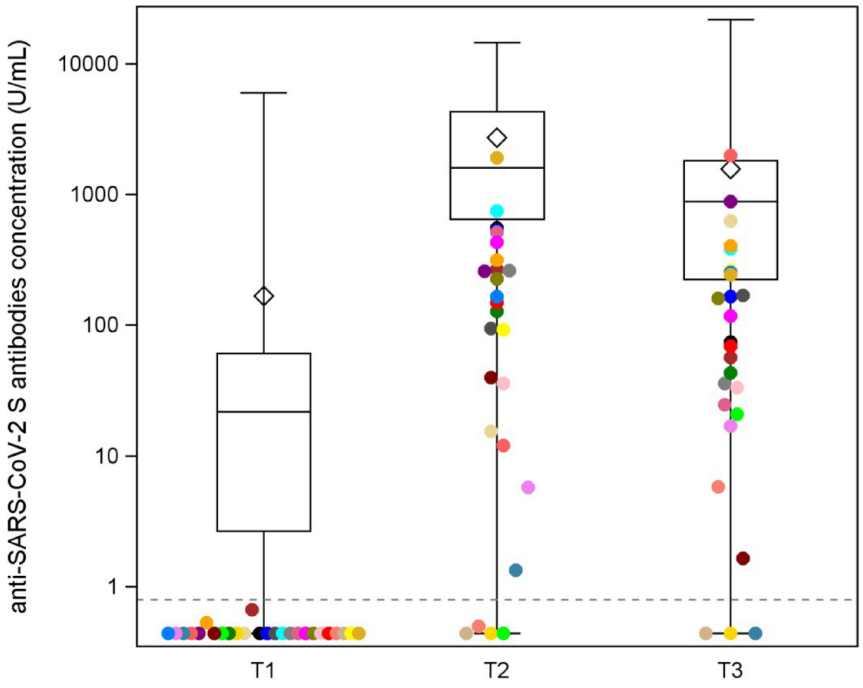

Figure 1. Distribution of the anti-spike antibody levels at T1, T2, and T3. Distributions of the antibody titer of the 171 patients at different timepoints (T1, T2, and T3). Each box indicates the 25th and 75th percentiles. The horizontal line and the diamond inside the box indicate the median and the mean, respectively. Whiskers indicate the extreme measured values. Patients with a negative titer after the first dose (T1) are represented with different colors to identify them and evaluate their dynamics of seroconversion in T2 and T3.

In a subgroup of 171 patients, we had available information about the anti-spike antibody level at T3 (Supplemental Figure 1). The distributions of the antibody titer at each timepoint (T1, T2, and T3) are shown in Figure 1. Of these 171 patients, 168 patients (98.25%) were seroconverted at T3. Among the three patients with a negative titer at T3, only one patient had a positive titer at T2 and became seronegative at T3. The seroconversion dynamics after each dose and the corresponding clinicopathological characteristics, anticancer treatment class, and different mRNA anti-SARS-CoV-2 vaccines received are reported in Supplemental Table 2.

Determinants of humoral immune response after mRNA anti-SARS-CoV-2 vaccination in patients with solid tumors

The ANOVA results on the roles of the variables of interest on the titer after the second dose of vaccine are reported in Table 2. Age, tumor type, and anticancer treatment class had a significant effect on the anti-spike antibody levels at T2. Younger patients had higher levels of antibodies (Supplemental Figure 2(a)) as compared with older patients, whereas patients with melanoma had the highest median levels, followed by patients with gastrointestinal tumors and neuroendocrine tumors (Supplemental Figure 2(b)). Moreover, patients receiving chemotherapy (alone or in combination with immunotherapy or radiotherapy) showed a lower level of antibodies as compared with those undergoing immunotherapy alone (contrast $p=0.0006$), biological therapy (alone or in combination with immunotherapy) (contrast $p=<0.0001$), or those who were not receiving any anticancer treatment (contrast $p=0.0093$) (Supplemental Figure 2(c)). Of note, the type of vaccine had no impact on the anti-spike antibody levels at T2 (Table 2). Following a backward procedure, the final multivariate model for the titer after the second dose of vaccine included only age and anticancer treatment class ($p=0.0230$ and $p<0.0001$, respectively) (Table 2). By pursuing the analysis according to the type of chemotherapy (platinum based *versus* non-platinum based), we did not find any difference in terms of antibody levels ($p=0.0833$) as well as in terms of seroconversion rate ($p=0.2575$) (Supplemental Figure 3(a) and (b)). Similarly, no statistically significant differences were observed between

Table 2. Results of univariate and multivariate analyses.

	T2 analysis ($n=243$)		Δ_{T3-T2} analysis ($n=171$)	
	Univariate analysis	Final multivariate model	Univariate analysis	Final multivariate model
	p Value	*p* Value	*p* Value	*p* Value
Sex	0.1665	–	0.0042	0.0017
Type of vaccine	0.0832	–	0.0381	0.0068
Stage of tumor	0.6744	–	0.4440	–
Type of tumor	0.0072	–	0.0102	–
Treatment	0.0001	<0.0001	0.0114	0.0118
Age	0.0174	0.0230	0.7397	–

chemo-immunotherapy and chemotherapy alone subgroups, both in terms of antibody levels ($p=0.9069$) and seroconversion rate ($p=0.4259$) (Supplemental Figure 3(c) and (d)). In addition, by focusing on the specific classes of biological therapies (Supplemental Figure 3(e)), we found that patients treated with poly (ADP-ribose) polymerase (PARP) inhibitors ($N=6$) showed the lowest median value of antibody levels, and a statistically significant difference was observed when compared with tyrosine kinase inhibitors (TKIs) (contrast $p=0.0042$), monoclonal antibodies/antibody–drug conjugates (contrast $p=0.0061$), or somatostatin analogs (contrast $p=0.0031$).

By analyzing the difference between antibody levels at T3 and T2, we found that sex, type of vaccine, type of tumor, and class of antitumor treatment significantly contributed to the modulation of the antibody levels at T3 (Table 2 and Figure 2). We observed a global decrease in the titer of antibodies between T2 and T3. The decrease was slighter in women, in patients receiving the mRNA-1273 vaccine and in patients with types of tumors that predominantly affect women (Supplemental Figure 4(a)–4(c)). Interestingly, patients receiving immunotherapy or not receiving any anticancer treatment had a more pronounced decrease in antibody levels compared with patients undergoing chemotherapy (contrast $p=0.0026$; contrast $p=0.0348$, respectively) (Supplemental Figure 4(d)).

The final multivariate model for the difference between antibody levels between T3 and T2, following a backward procedure, included the following variables: sex, type of vaccine, and anticancer treatment class ($p=0.0017$, $p=0.0068$, and $p=0.0118$, respectively) (Table 2).

We then resorted to a mixed model and we found that the time factor (as well as each time contrast) resulted in a statistically significant ($p<0.0001$) longitudinal effect (as depicted in Supplemental Figure 5(a)), with a significant difference in the trends between younger and older patients ($p=0.0082$, see Supplemental Figure 5(b)). Interestingly, we found significant interactions between time and sex ($p=0.0120$), as well as between time and different anticancer treatment class ($p=0.0484$) as represented in Supplemental Figure 5(c) and 5(d).

Figure 3 shows the median percentage changes in the antibody levels between T1 and T2 and between T2 and T3 for each category of the variables of interest. Considering as reference the overall median percentage changes, the highest increment between T1 and T2 was observed for patients with a negative titer after the first dose, followed by patients with head and neck cancer and patients undergoing chemotherapy. Interestingly, head and neck cancer patients were also those with the highest decrement of titer between T2 and T3, followed by patients with genitourinary tumors and patients receiving immunotherapy.

Discussion

Understanding the dynamics of the humoral immune response in cancer patients after mRNA anti-SARS-CoV-2 vaccination is crucial to optimally plan the next steps of an effective SARS-CoV-2 mitigation/control strategy in such

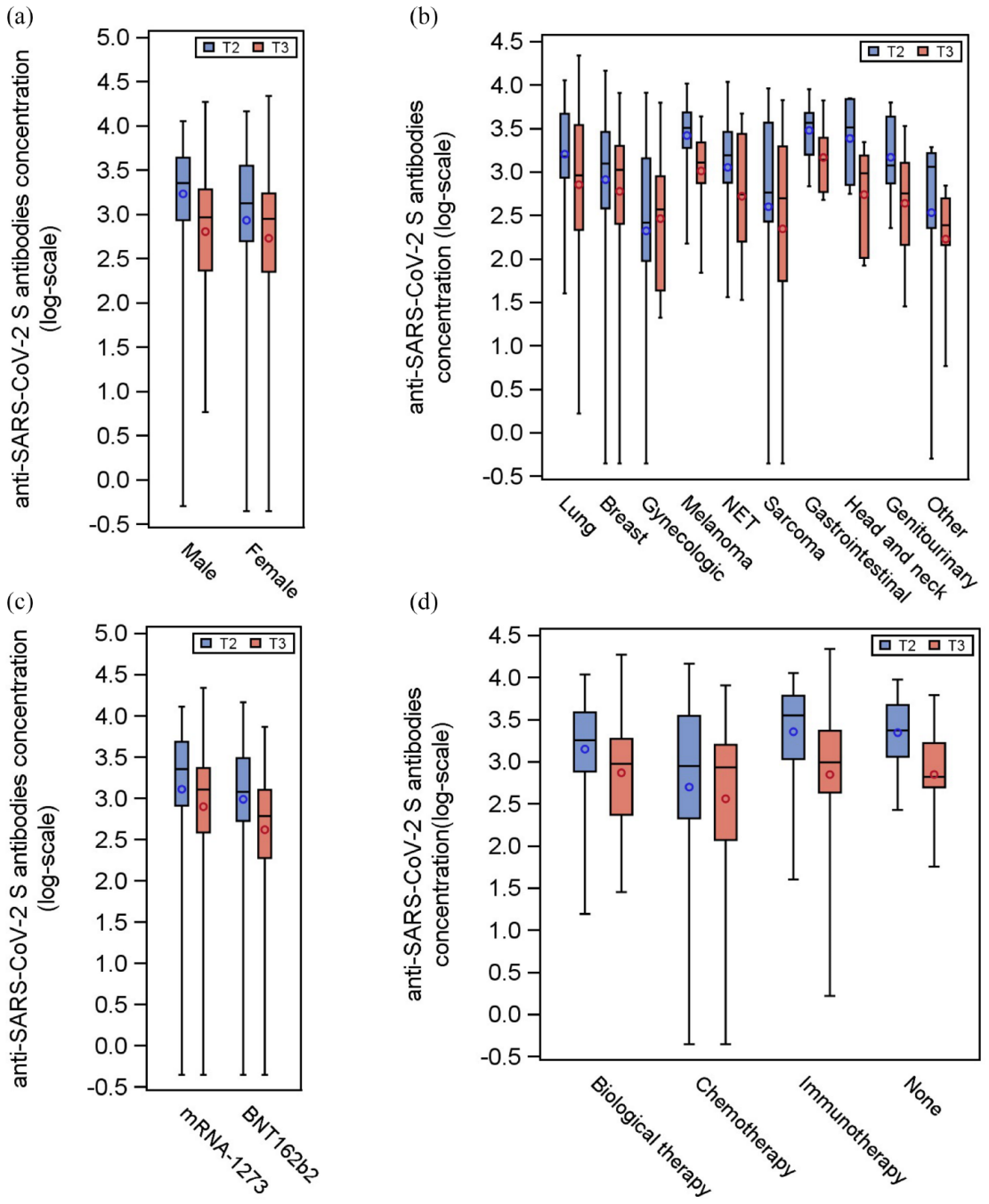

Figure 2. Distributions of the anti-spike antibody levels at T2 and T3 according to selected variables. Distributions of the antibody titer of the 171 patients at T2 (blue box) and T3 (red box), according to sex (panel a), type of tumor (panel b), type of vaccine (panel c), and anticancer treatment class (panel d). Each box indicates the 25th and 75th percentiles. The horizontal line and the circle inside the box indicate the median and the mean, respectively. Whiskers indicate the extreme measured values.

population of fragile patients.[11] In the present study, we observed an optimal response after two doses of mRNA vaccine in patients with solid tumors, with a rate of seroconversion that was comparable to that of a matched control population of healthy subjects, in line with the recently reported data of a prospective, multicenter, non-inferiority trial.[12] Of note, the 97.94% rate of seroconversion after the second dose of vaccination observed in our study population was higher than the rates reported in similar

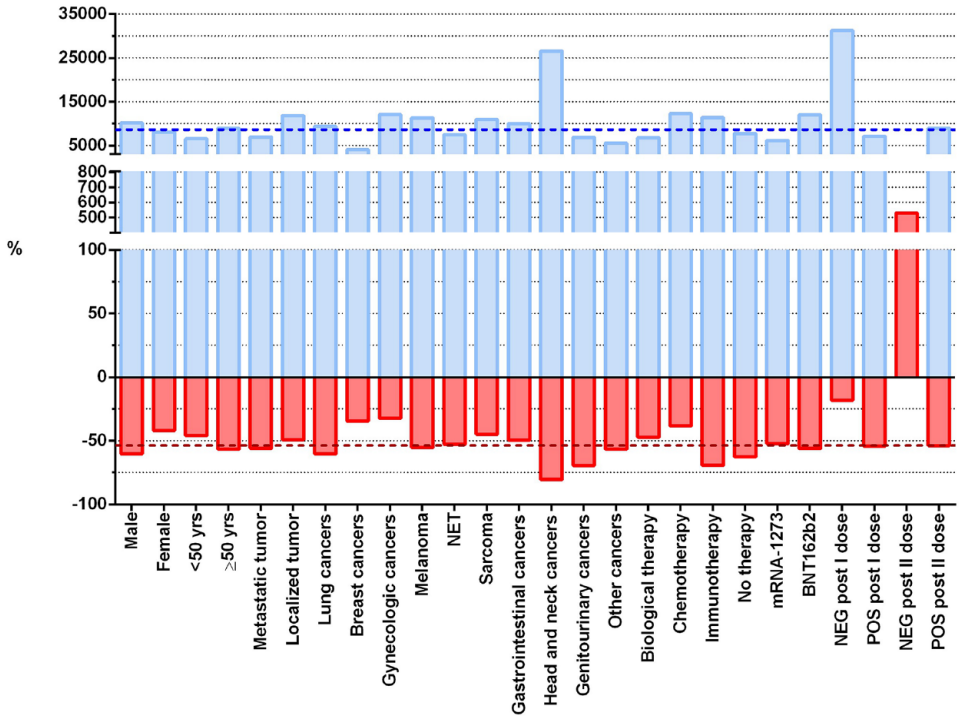

Figure 3. Percentage changes in the antibody levels between T1, T2 and T2, T3. Each blue and red bar represents the median percentage change between T2 and T1 or between T3 and T2, respectively, in each category of the variables of interest. The blue and red dotted reference lines indicate the overall median percentage change for the T2 – T1 and T3 – T2 differences, respectively.

populations.[13–15] The efficacy of anti-SARS-CoV-2 vaccination in patients with solid tumors (in terms of seroconversion and humoral response) seems better than in patients with hematological malignancies, as an indirect comparison with our previously reported data suggests (seroconversion rate in patients with hematological malignancies: 64.6% after two doses of mRNA vaccine),[16] and in line with the literature data.[17] These differences may be explained by the peculiar suppression of the B-cell immune response that characterizes hematological malignancies (as compared with solid tumors) and that is driven by intrinsic biological features and specific anticancer treatments (i.e. anti-CD20 monoclonal antibodies used in lymphoid malignancies).[16] Regarding the impact of concomitant anticancer treatments on the efficacy of mRNA vaccination in our population of patients with solid tumors, we did not observe a difference in the rate of seroconversion according to the type of concomitant treatment, even if the titer of antibodies after the second dose of vaccine was lower for patients receiving cytotoxic chemotherapy, consistently with the recent data on the negative impact of multiple-agent cytotoxic chemotherapy on post-vaccination anti-SARS-CoV-2 IgG titer in cancer patients.[18–22] In the subset of patients treated with biological therapies, patients treated with PARP inhibitors showed the lowest median value of anti-SARS-CoV-2 IgG levels, in line with the evidence that PARP deficiency may impair peripheral B-cell homeostasis and humoral response.[23] Interestingly, even if immunotherapy does not seem to affect the rate of seroconversion in cancer patients as previously reported,[24,25] the more pronounced decrease in antibody levels in the late timepoint that we observed in patients receiving immune checkpoint inhibitors was consistent with two other reports about sustained antibody levels in cancer patients receiving immunotherapy-based treatments at the time of vaccination.[26,27] A possible explanation is that immune checkpoint inhibitors may have a positive acute effect, favoring a higher peak of antibody levels soon after the second dose, thus exaggerating the decrease in antibodies at late timepoints. However, there is a need to fully understand the interplay between immune checkpoint inhibitors and the humoral immune response to mRNA vaccination in cancer patients. Finally, regarding the impact of the type of tumor, the observed highest median levels of anti-spike antibody levels at T2 in patients with melanoma may be explained, at least in part, by the

fact that none of these patients received chemotherapy (associated with a low titer of antibodies at T2), whereas about 40% of the patients received immune checkpoint inhibitors (associated with a high titer of antibody at T2). We acknowledge that (i) the lack of data on cellular anti-SARS-CoV-2 immunity upon vaccination and (ii) the lack of data on the dynamics of antibodies titer modulation after a third booster dose of vaccine are the major limitations of the present study, but the availability of data regarding a late timepoint (three months) after the second dose of vaccination adds new valuable insights on the longitudinal dynamics of humoral response to mRNA vaccines in patients with solid tumors.

In conclusion, the systemic immunosuppression characterizing cancer patients did not seem to dramatically affect the humoral response to anti-SARS-CoV-2 mRNA vaccines in our population of patients with solid tumors. The seroconversion rate of cancer patients was very high and comparable to that of healthy subjects. Our data confirm that the class of concomitant anticancer treatment may modulate the degree of the humoral response (in terms of antibody titer) but does not affect the seroconversion rate. Further investigations are needed to dissect the interplay between current immunotherapy (i.e. immune checkpoint inhibitors) and the longitudinal dynamics of humoral response to mRNA vaccines, as well as to analyze the cellular response to mRNA vaccines in cancer patients.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplemental material

Supplemental material for this article is available online.

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