


LETTER TO THE EDITOR

Open Access



Low titers of SARS-CoV-2 neutralizing antibodies after first vaccination dose in cancer patients receiving checkpoint inhibitors

Evangelos Terpos^{1*} , Flora Zagouri¹, Michalis Liontos¹, Aimilia D. Sklirou², Konstantinos Koutsoukos¹, Christos Markellos¹, Alexandros Briasoulis¹, Eleni-Dimitra Papanagnou², Ioannis P. Trougkos² and Meletios-Athanasios Dimopoulos¹

Abstract

Vaccination for SARS-CoV-2 provides significant protection against the infection in the general population. However, only limited data exist for patients with cancer under systemic therapy. Based on this, our site has initiated a study evaluating safety and efficacy of SARS-CoV-2 vaccination in patients with solid and hematological malignancies under several systemic therapies. The initial results of the cohort of 59 patients receiving Immune Checkpoint Inhibitors are presented here. Despite no new safety issues have been noticed, the levels of SARS-CoV-2 neutralizing antibodies are significantly lower in comparison to matched healthy volunteers up to day 22 post the first dose. These results should be taken into consideration for the patients under treatment.

Keywords: SARS-CoV-2, Vaccination, Cancer, Immune checkpoint inhibitors, BNT162b2, AZD1222

To the Editor,

Patients with cancer are considered vulnerable to SARS-CoV-2 infection [1] and have been prioritized in the vaccination process in several countries including Greece. In addition, international oncological societies favored COVID-19 vaccination for cancer patients on the basis of risk and benefits evaluation of all available data. However, patients with cancer were excluded from SARS-CoV-2 vaccines registrational trials [2, 3] and we lack data regarding the safety and efficacy of vaccination in this population. Under this perspective, we undertook a large prospective study (NCT04743388) enrolling patients with solid cancers, hematologic malignancies

as well as healthy volunteers for the kinetics of anti-SARS-CoV-2 antibodies after COVID-19 vaccination [4]. Herein, we report the development of neutralizing antibodies (NABs) against SARS-CoV-2 in patients with solid tumors receiving immune checkpoint inhibitors (ICIs) after the first dose of the BNT162b2 and AZD1222 vaccines. Major inclusion criteria for this cohort of the study included: (1) age above 18 years; (2) presence of solid organ malignancies treated with immunotherapy irrespective of the treatment phase; and (3) eligibility for vaccination.

The serum of both patients and controls was collected on day 1 prior to vaccination and on day 22. NABs against SARS-CoV-2 were measured using FDA approved methodology (ELISA, cPass™ SARS-CoV-2 NABs Detection Kit; GenScript, Piscataway, NJ, USA) [5] on the above-mentioned timepoints. Samples of the same patient or control were measured in the same ELISA plate. The study was approved by the respective Ethical Committees in accordance with the Declaration of Helsinki and the

*Correspondence: eterpos@med.uoa.gr

¹ Department of Clinical Therapeutics, School of Medicine, Alexandra General Hospital, National and Kapodistrian University of Athens, 80 Vas. Sofias Avenue, 11528 Athens, Greece

Full list of author information is available at the end of the article



© The Author(s) 2021. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

International Conference on Harmonization for Good Clinical Practice. All patients and controls provided written informed consent prior enrollment in the study. Baseline demographics, co-morbidities, and the NAb levels were compared between the 2 groups, Chi-square test for categorical variables and unpaired t-test or Wilcoxon signed-rank test (as appropriate) for continuous variables. To adjust for potential confounding effects of differences in covariates, we used case-control matching to match the two groups for age, gender, and type of vaccine with the calipmatch command in Stata. All data extraction and analyses were conducted using Stata 16.0 (StataCorp 2019, Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). Two-sided p value < 0.05 was used for statistical significance.

Study population included 59 patients (36 males/23 females; median age: 66 years, IQR 61–76 years) and 283 controls (median age: 64 years, IQR 59–82 years, $p=0.75$ for age compared with patients), vaccinated during the same period. 44/59 patients (74.6%) and 232/283 controls (82%) were vaccinated with a mRNA vaccine (BNT162b2 or mRNA-1273), while the remaining received the AZD1222 vaccine ($p=0.19$). The characteristics of the patients are depicted in Table 1. Among patients, 16 had lung cancer, 15 bladder cancer, 11 kidney carcinoma, and the remaining 17 other carcinomas. Most patients (49 patients, 83.0%) received anti-PD1 treatment, while 10 (17.0%) received anti-PD-L1 antibodies or immunotherapy combination. Comorbidities in the patient group included cardiovascular disease in 42.4%, diabetes in 20.3%, pulmonary disease in 10.2%.

On D1, two patients (3.4%) and 26 (9.2%) controls had NAb titers of $\geq 30\%$ (positivity cut-off); there was no difference regarding the NAb titers between patients and controls on D1 ($p=0.35$). None of them had a prior history of known COVID-19. After the first vaccine dose, on D22, patients had lower NAb titers compared to controls: the median NAb inhibition titer was 22% (IQR 13.4–30.2%) for patients versus 38% (IQR 23–54%) for controls; $p<0.001$ (Fig. 1). More, specifically, 15 (25%) patients versus 186 (65.7%) controls developed NAb titers $\geq 30\%$ on D22 ($p<0.001$). The respective number of patients and controls who developed NAb titers $\geq 50\%$ (clinically relevant viral inhibition [6]) was 6 (10.7%) and 93 (32.9%), respectively ($p=0.01$). Of note, none of the patients enrolled had neutropenia or lymphopenia at first vaccination dose (Additional file 1: Table S1).

Recently, Waissengrin et al. [7] reported the safety results of BNT162b2 vaccine in patients with cancer treated with ICIs. We confirm these data in our study population; amongst the 59 patients of our department who received vaccination while on treatment with ICIs, no unexpected adverse events were noted. During the

Table 1 Characteristics of the patients

Characteristic	Total population
	Median (IQR)
Age	66 (61–76)
BMI	26.1 (23.6–28.3)
	<i>N</i> (%)
Sex	
Male	36 (61.0%)
Female	23 (39.0%)
Type of cancer	
Lung cancer	16 (27.1%)
Bladder cancer	15 (25.4%)
Kidney cancer	11 (18.6%)
Uterine cancer	5 (8.5%)
Pancreatic cancer	3 (5.1%)
Other	8 (13.6%)
Missing	1 (1.7%)
Type of therapy	
Anti-PD1	49 (83.0%)
Anti-PD-L1	8 (13.6%)
I/O combo	2 (3.4%)
Vaccine	
BNT162b2	41 (69.5%)
AZD1222	15 (25.4%)
mRNA-1273	3 (5.1%)
Vaccine-related adverse events	
None	37 (62.7%)
Fever	1 (1.7%)
Pain at injection site	11 (18.6%)
Fatigue	3 (5.1%)
Other	1 (1.7%)
Comorbidities	
Yes	39 (66.1%)
None	11 (18.6%)
Missing	9 (15.3%)

IQR interquartile range, BMI body mass index, I/O Immunotherapy

post vaccination follow-up period (median 44 days, IQR 36–67 days) immunotherapy related adverse events were recorded in one patient (1.7%). For the first time, we also report that patients on treatment with ICIs receiving the first dose of the BNT162b2 and AZD1222 vaccines develop low titers of NAb against SARS-CoV-2 by day 22. These results could be attributed to the immunosuppressive effect of cancer and/or treatment given and inform regarding the optimal management of these patients at least until vaccination completion. Further follow-up of the current study will provide significant data for the efficacy of vaccination in cancer patients.

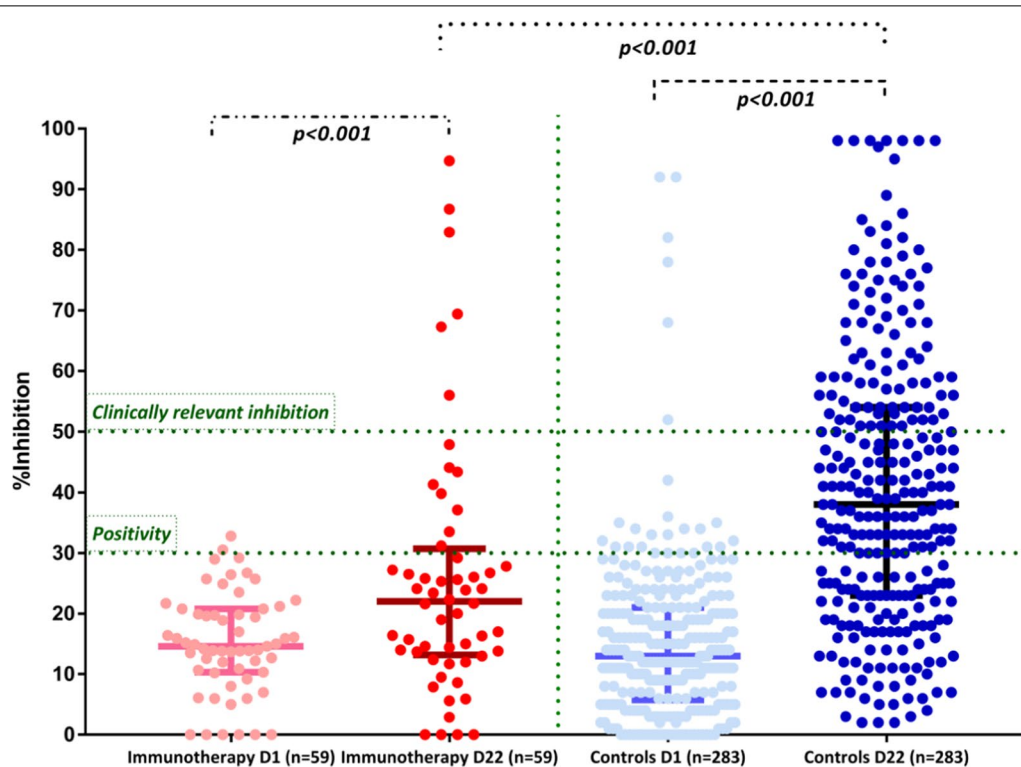


Fig. 1 Kinetics of neutralizing antibodies in patients receiving immunotherapy and matched controls after vaccination with the first dose of the BNT162b2, mRNA-1273 and AZD1222 vaccine. On D22, patients had lower production of NAb inhibition titers compared to controls of similar age and gender (see text). Only 6 patients (10.7%) had NAb titers of equal or more than 50%

Abbreviations

ICIs: Immune checkpoint inhibitors; NAbs: Neutralizing antibodies; IQR: Inter-quartile range.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13045-021-01099-x>.

Additional file 1. Table S1: Detailed characteristics of patients

Acknowledgements

We thank Abis Cohen MD; Ioanna Charitaki, RN; Ioanna Katsiana RN; Tina Bagratuni, PhD; Christine Ivy Liacos, PhD; Nikoletta-Aikaterini Kokkali, RN; Nefeli Mavrianou-Koutsoukou, PhD; Dimitrios Patseas, PhD and Mrs Stamatia Skourti for administrative, technical, or material support; Sentiljana Gumeni, PhD for acquisition, analysis, or interpretation of data. We also thank SYN-ENOSIS (Greece), AEGEAS (Greece) and IEMBITHKEK (Greece) for partially funding this study, as well as all of the study participants for donating their time and samples.

Authors' contributions

ET designed research, performed research, analyzed data and wrote the paper. IPT and MAD contributed vital new reagents or analytical tools, performed research, analyzed data, reviewed all paper drafts and gave approval to final version. FZ, ML, ADS, KK, CM, AB, EDP performed research, analyzed data, reviewed all paper drafts and gave approval to final version. All authors read and approved the final manuscript.

Funding

SYN-ENOSIS (Greece), AEGEAS (Greece) and IEMBITHKEK (Greece) partially funded this study.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information file.

Declarations

Ethics approval and consent to participate

Described within the letter. The study was approved by the respective Ethical Committees (Alexandra Hospital Ethics Committee, Reference Number: 900/24-12-2020) in accordance with the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice. All patients and controls provided written informed consent prior enrollment in the study.

Consent for publication

Not applicable.

Competing interests

We declare no competing interests.

Author details

¹Department of Clinical Therapeutics, School of Medicine, Alexandra General Hospital, National and Kapodistrian University of Athens, 80 Vas. Sofias Avenue, 11528 Athens, Greece. ²Department of Cell Biology and Biophysics, Faculty of Biology, National and Kapodistrian University of Athens, Athens, Greece.

Received: 28 April 2021 Accepted: 26 May 2021
Published online: 31 May 2021

References

1. Lee LYW, Cazier J-B, Angelis V, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. *The Lancet*. 2020;395(10241):1919–26.
2. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603–15.
3. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *The Lancet*. 2021;397(10269):99–111.
4. Terpos E, Trougakos IP, Apostolou F, et al. Age- and gender-dependent antibody responses against SARS-CoV-2 in health workers and octogenarians after vaccination with the BNT162b2 mRNA vaccine. *Am J Hematol*. 2020;6:66.
5. Tan CW, Chia WN, Qin X, et al. A SARS-CoV-2 surrogate virus neutralization test based on antibody-mediated blockage of ACE2–spike protein–protein interaction. *Nat Biotechnol*. 2020;38(9):1073–8.
6. Walsh EE, Frenck RW Jr, Falsey AR, et al. Safety and immunogenicity of two RNA-based Covid-19 vaccine candidates. *N Engl J Med*. 2020;383(25):2439–50.
7. Waissengrin B, Agbarya A, Safadi E, Padova H, Wolf I. Short-term safety of the BNT162b2 mRNA COVID-19 vaccine in patients with cancer treated with immune checkpoint inhibitors. *Lancet Oncol*. 2020;6:66.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

