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LETTERS TO THE EDITOR

High seroconversion rate but low antibody titers after two injections of BNT162b2 (Pfizer-BioNTech) vaccine in patients treated with chemotherapy for solid cancers

Recent data, including ours, show that patients treated for solid cancers (SCs) had low anti-spike antibody responses after a first dose of messenger RNA (mRNA) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine, with seroconversion rates ranging from 38% to 55%, in comparison with healthy controls having seroconversion rates ranging from 94% to 100%.[1-3] This humoral response was more impaired in elderly and chemotherapy-treated patients. In this study we aimed to compare the proportion and the level of antibody response 3-4 weeks after the second injection of the BNT162b2 (Pfizer-BioNTech) vaccine in patients with SCs using healthy volunteers (HVs) as a control population.

Patients with SCs on active treatment or who received treatment in the past 2 years and HVs who underwent SARS-CoV-2 vaccination between 5 January 2021 and 2 April 2021 at the Pitié-Salpêtrière and Tenon hospitals, Paris, France, and at the Saint Jean Polyclinic, Nice, France, were selected for analysis. The titration of anti-SARS-CoV-2 antibodies was proposed 3-4 weeks after the second injection of BNT162b2 (Pfizer-BioNTech) vaccine. Anti-spike antibodies were detected using different assays (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.06.018). For quantitative analysis, only titrations using the Abbott Alinity SARS-CoV-2 immunoglobulin (Ig) G chemiluminescent microparticle immunoassay (detection threshold: 50 UA/ml), and the Roche Elecsys SARS-CoV-2 total Ig electrochemiluminescent immunoassay (detection threshold: 0.8 U/ml) were analyzed. Median titers of anti-spike antibodies were compared between patients with SCs and HVs, and between different subpopulations of patients using Kruskal-Wallis tests. This study was approved by the 'Commission Nationale de l'Informatique et des Libertés' (MR004, registration number: 2221945).

No patients had prior exposure to COVID-19 as none of them had IgG anti-nucleoprotein before vaccination. SARS-CoV-2 antibodies were measured in 223 patients and 49 HVs (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.06.018). The median age of patients was 67 years [interquartile range (IQR) 60-75 years], with 142 women (64%) and 81 men (36%). 129 (58%) patients were treated with chemotherapy at the time of vaccination. The seroconversion rate was 94% in patients and 100% in HVs. The 13/223 (6%) non-seroconverter patients were 8 women and 5 men, with ages ranging from 45 to 90 years, mostly metastatic ($n = 8$), including 10/13 treated with chemotherapy. Titers of anti-spike antibodies were significantly lower in patients with SCs in comparison with HVs, and significantly lower in those receiving chemotherapy (in combination or not with other treatments as targeted therapies), regardless of the assay used (Figure 1). Titers of anti-spike antibodies did not differ depending on age, sex, cancer location and metastatic status. Only one mild case of COVID-19 occurred after the first injection of vaccine, in a patient with colon cancer.

In summary, the mRNA vaccine boost led to a high seroconversion rate, reinforcing the need not to delay the second dose. However, anti-spike antibody titers were 3-10 times lower in patients with SCs than in healthy controls, raising concerns about impaired humoral immunity, especially in patients treated with chemotherapy. At the same time, the seroconversion data are rather reassuring among patients on anti-Human Epidermal Growth Factor Receptor 2, anti-Programmed cell death protein 1/Programmed death-ligand 1, antiangiogenic treatment or hormone therapy without associated chemotherapy. Nevertheless, correlates of immunity to SARS-CoV-2 are still not defined, and further studies are required to determine the SARS-CoV-2 correlates of vaccine-induced protection based on neutralizing antibodies and cellular immunity.[4] We still lack the insight required to determine when a third dose (second booster) should be offered to patients with SCs.

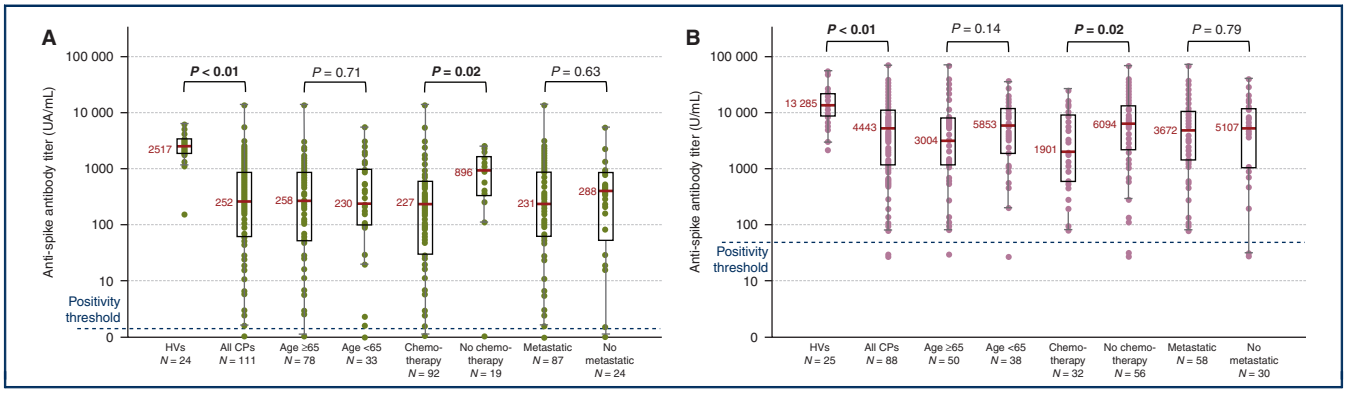

Figure 1. Anti-spike antibody titers in HVs and cancer patients (CPs), using Roche Elecsys assay (A) and Abbott Alinity assay (B).
HVs, healthy volunteers.

Pending additional data, we would highly recommend vaccination for family and friendship circles, to provide an indirect protection against COVID-19 to this population.

R. Palich[1*†], M. Veyri[2,†], A. Vozy[2], S. Marot[3], J. Gligorov[4], M.-A. Benderra[4], P. Maingon[5], L. Morand-Joubert[6], Z. Adjoutah[7], A.-G. Marcelin[3], J.-P. Spano[2] & J. Barrière[8]

[1]*Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique (iPLESP), Assistance Publique-Hôpitaux de Paris (AP-HP), Pitié Salpêtrière Hospital, Departments of Medical Oncology and Infectious Diseases, Paris;*
[2]*Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique (iPLESP), Assistance Publique-Hôpitaux de Paris (AP-HP), Pitié Salpêtrière Hospital, Department of Medical Oncology, Institut Universitaire de Cancérologie (IUC), CLIP[2] Galilée, Paris;*
[3]*Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique (iPLESP), Assistance Publique-Hôpitaux de Paris (AP-HP), Pitié Salpêtrière Hospital, Department of Virology, Paris;*
[4]*Sorbonne Université, Assistance Publique-Hôpitaux de Paris (AP-HP), Tenon Hospital, Department of Medical Oncology, Inserm U938, Institut Universitaire de Cancérologie (IUC), CLIP[2] Galilée, Paris;*
[5]*Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique (iPLESP), Assistance Publique-Hôpitaux de Paris (AP-HP), Pitié Salpêtrière Hospital, Department of Oncology Radiotherapy, Institut Universitaire de Cancérologie (IUC), CLIP[2] Galilée, Paris;*
[6]*Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique (iPLESP), Assistance Publique-Hôpitaux de Paris (AP-HP), Saint Antoine Hospital, Department of Virology, Paris;*
[7]*Department of Biology, Cerballiance, Cagnes-sur-Mer;*
[8]*Department of Medical Oncology, Polyclinique Saint Jean, Cagnes-sur-Mer, France*
(*E-mail: romain.palich@aphp.fr).

†These authors contributed equally to this work.

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Plitidepsin for the management of a cancer patient infected with SARS-CoV-2 while receiving chemotherapy

Plitidepsin is a cyclic peptide that inhibits the host protein elongation factor alpha 1 (EF1A), thus blocking viral replication. A hospitalized patient with stage IIIB gastric signet ring cell carcinoma and multiple comorbidities developed COVID-19 shortly after receiving his first chemotherapy course. He was treated with plitidepsin on a compassionate use basis. The patient showed a substantial acute reduction in viral load 4 days after initiating plitidepsin treatment and was negative for SARS-CoV-2 by day 14. Therapy was well tolerated, and no COVID-19-related complications were observed. The patient was discharged 18 days after plitidepsin treatment, having received a full second course of chemotherapy, with only a 1-week delay from the planned schedule.

Patients with cancer who are also infected with SARS-CoV-2 have a poor prognosis and increased risk of all-cause mortality.[1-3] Furthermore, cancer treatments are almost always withheld from patients with COVID-19, leading to an increased risk of tumor-related morbidities, and potential onset of progressive disease in the absence of therapy.

Recently, a study with plitidepsin in adults with SARS-CoV-2 infection and who requiring hospital admission assessed that the discharge rates by days 8 and 15 after the start of plitidepsin were 56.8% and 81.8%, respectively.[4] Likewise, a mean -4.2 $\log^{10}$ reduction in viral load from baseline was attained by day 15.

The antiviral mechanism of action of plitidepsin is mediated through inhibition of the host protein EF1A.[5] Notably, the nucleocapsid protein of SARS-CoV-2 has been shown to interact directly with EF1A and is essential for viral replication as demonstrated by a significant reduction in viral replication capability following EF1A knockdown.