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Letter

Immunogenicity of a heterologous COVID-19 vaccine after failed vaccination in a lymphoma patient

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We read with great interest the recent publications in *Cancer Cell* regarding seroconversion rates following SARS-CoV-2 vaccination among patients with cancer (Addeo et al., 2021; Thakkar et al., 2021). Both studies demonstrated that a lower proportion of patients with hematologic malignancies seroconverted. Additionally, these individuals had lower absolute antibody titers. Similar data have emerged from other studies, some showing even lower seroconversion rates of 50%–60% in patients with hematologic malignancies (Herishanu et al., 2021). Seroconversion to other standard vaccinations is known to be relatively poor in this population, with rates of ~50% or lower in patients with chronic lymphocytic leukemia, for example, especially in those receiving agents such as Bruton's tyrosine kinase inhibitors (BTKis) or anti-B cell antibody therapies (Pleyer et al., 2021).

These observations are important given that individuals with hematologic malignancies have a high incidence of morbidity and mortality from COVID-19 (Mato et al., 2020), likely due to advanced age, comorbidities, and disease- and/or treatment-related immune dysfunction. Thus, as the authors emphasize, there is a critical need to determine better vaccination strategies in immunocompromised individuals. There is clinical precedent for higher-, additional-, or heterologous-dose strategies for standard and SARS-CoV-2 vaccines in other contexts (Cardell et al., 2008; Hillus et al., 2021; Werbel et al., 2021), but to the authors' knowledge, there are no reports of these approaches using SARS-CoV-2 vaccines in cancer patients.

Here, we describe a 59-year-old man with lymphoplasmacytic lymphoma who received four doses of rituximab (anti-CD20) in November 2016 and subsequently began daily ibrutinib (a BTKi) in November 2017, achieving a partial response. He switched to zanubrutinib (an alternative BTKi) in July 2020 due to intolerance with ibrutinib. He received the standard two doses of the BNT162b2 mRNA vaccine (Pfizer/BioNTech) in February and March of 2021. An EUA-authorized semiquantitative total antibody assay (Roche Elecsys Anti-SARS-CoV-2 S) against the spike protein receptor binding domain was assessed five weeks after the second dose and was undetectable at <0.4 arbitrary units (AU)/mL (>0.79 AU/mL is considered positive, and 250 AU/mL is the undiluted upper limit, which may be reported up to 2,500 AU/mL or 25,000 AU/ML for 10-fold or 100-fold diluted samples). A qualitative anti-nucleocapsid assay (Roche Elecsys Anti-SARS-CoV-2 N) was also negative.

The patient independently sought out and received a third vaccination with the JNJ-78436735 viral vector vaccine (Johnson & Johnson) 10 weeks after his second dose of the BNT162b2 mRNA vaccine. He reported mild malaise and headache starting 1 day post-vaccination, and that resolved by the following day. Subsequent testing with the same assay 18 days later demonstrated seroconversion based on an anti-spike protein total antibody titer of 215 AU/mL. Repeat testing 3 days later demonstrated a negative anti-nucleocapsid antibody and a positive anti-spike protein total antibody titer of 207 AU/mL on the same assays described above. A D614G SARS-CoV-2 spike pseudotyped lentivirus neutralization assay resulted in a 50% neutralization dose (ND_{50}) of 242, corresponding to 51 international units (IU)/mL using the WHO International Standard for anti-SARS-CoV-2 antibody (Table S1; Crawford et al., 2020). Laboratory results prior to and after vaccinations demonstrated less-than-normal/low-normal white blood cell counts, lymphocyte counts, and immunoglobulins (Table S1). He did not receive immunoglobulin replacement therapy in the interim.

This case suggests that heterologous vaccination against SARS-CoV-2 may yield measurable antibody-mediated immunity in immunocompromised patients despite low B cell levels. Homologous booster doses may be similarly efficacious. However, this individual's antibody titer after a third dose remained lower than typically observed with this assay in healthy individuals or those with solid tumors, with most people generating titers >1,000 AU/mL (Addeo et al., 2021; Bradley et al., 2021; Herishanu et al., 2021). As of this writing, we are unaware of reports of safety or immunogenicity of mixed COVID-19 vaccine regimens in cancer patients. Limitations of this report include that it is a single case, and we do not present data pertaining to cellular immunity. Nonetheless, these results, along with emerging data of impaired immunogenicity of primary SARS-CoV-2 vaccine series in immunocompromised patients, underscore the urgent need to perform trials assessing alternative vaccination strategies in high-risk populations.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2021.06.015.

DECLARATION OF INTERESTS

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Supplemental information

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Supplemental information

Table S1. Immunologic markers and SARS-CoV-2 antibody response in a 59-year-old man with lymphoplasmacytic lymphoma receiving a Bruton's tyrosine kinase inhibitors (BTKi)

	Pre-vaccine 1 (BNT162b2 mRNA)	**Pre-vaccine 2** (BNT162b2 mRNA)	**Post-vaccine 2**	**Post-vaccine 3** (JNJ-78436735, viral vector)
Anti-SARS-CoV-2 spike protein total antibody titer (AU/mL)[a]	NA	NA	<0.4	215
Anti-SARS-CoV-2 neutralilzing antibody titer (ND_{50})[a]	NA	NA	NA	242
WBC (10^3 cells/uL)[b]	3.68	3.51		4.48
ALC (10^3 cells/uL)[b]	1.55	1.41		1.89
IgG (mg/dL)[c]	587	NA		585
IgM (mg/dL)[c]	180	NA		189
IgA (mg/dL)[c]	94	NA		101
CD3+/CD4+ T cells (cells/uL)[d]	NA	NA		1,039
CD3+/CD8+ T cells (cells/uL)[d]	NA	NA		489
CD19+ B cells (cells/uL)[d]	NA	NA		2

WBC, white blood cell count; ALC, absolute lymphocyte count; NA, not available.
[a]Testing was performed 35 days after vaccine 2 and 18 days after vaccine 3. The ND_{50} corresponds to the dilution of serum (1:242 in this case) resulting in 50% neutralization using a D614G SARS-CoV-2 spike protein pseudotyped lentivirus neutralization assay (Crawford et al., 2020). This is equivalent to an ND_{50} of 51 IU/mL based on a conversion factor for the WHO international units.
[b]WBC and ALC were collected 34 days prior to vaccine 1, 1 day prior to vaccine 2, and 12 days after vaccine 3. The lower limit of normal for WBC and ALC is 4.3 x 10^3 and 1.0 x 10^3 cells/uL, respectively.
[c]Total immunoglobulins were collected 58 days prior to vaccine 1 and 12 days after vaccine 3. The lower limits of normal for IgG, IgM, and IgA are 610, 40, and 84 mg/dL, respectively.
[d]Flow cytometry analyses were performed on a whole blood sample obtained 21 days after vaccine 3. The lower limits of normal for CD4+ T cells, CD8+ T cells, and B cells are 730, 250, and 160 cells/uL, respectively.