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COMMENTARY

Benefit of repeated COVID-19 vaccination for patients with B-cell malignancies

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Patients with B-cell malignancies under B-cell depletion have an increased risk of COVID-19 related morbidity and mortality and uncertainty has been existing about the efficacy of repeated COVID-19 vaccination among them. The translational study of Pinder and colleagues has depicted for the first time the entire immunologic and clinical picture of post-COVID-19 vaccination in patients with B-cell malignancies and underlined strongly the need for repetitive COVID-19 vaccination in this population, even in the case of previous failure to build up an adequate immune response.

During the period of the COVID-19 pandemic, the management of patients with B-cell malignancies has been challenging for haemato-oncologists, both due to immune dysfunction mediated by the lymphoma and also due to B-cell depletion under lymphoma treatment. So far, numerous and mostly heterogeneous series on lymphoma patients with COVID-19 have been published reporting mortality rates ranging up to 40% in the pre-vaccination era.[1]

With the advent of COVID-19 vaccination, the uncertainty further emerged when assessing the benefit of the vaccination for patients with B-cell malignancies under B-cell depleting treatment. In a retrospective series[2] of lymphoma patients receiving bispecific anti-CD20 B-cell antibodies such as blinatumomab, 30% of the patients experienced SARS-CoV-2 infection during treatment, despite the fact that the majority had received at least one dose of COVID-19 vaccine. More than 80% of these patients required treatment for COVID-19, with hospitalization being necessary in nearly 60%, and, remarkably, ICU admission rates around 20%.

Although several international studies identified the benefit of COVID-19 vaccination for patients with B-cell malignancies, for example the 100 day overall survival for vaccinated versus non-vaccinated Waldenström's macroglobulinaemia patients ($n = 190$) was 100% versus 82% ($p = 0.008$) and 97% versus 81% in the 2021–2022 period compared with 2020 ($p = 0.014$),[3] many questions remain open: Which patients with B-cell malignancy and at what time point benefit most from COVID-19 vaccines? What is the neutralizing capability of anti-SARS-CoV-2 antibodies post-COVID-19 vaccines in such immunologically compromised subjects? What is the interplay between B-, T- and NK-T cellular components following COVID-19 vaccination in these patients? Is it still worthwhile vaccinating patients with B-cell malignancy who failed to seroconvert to COVID-19 vaccines before?

Previous studies on the efficacy of COVID-19 vaccination in patients with B-cell malignancies have predominantly addressed distinct questions, as listed above, while not being able to address the entire immunologic and clinical picture of post-COVID-19 vaccination in this patient population. In the study "Humoral and cellular responses to SARS-CoV-2 in patients with B cell haematological malignancies improve with successive vaccination" published in the current issue of the *British Journal of Haematology*,

Pinder et al.[4] investigated the humoral and cellular response to COVID-19 vaccination in 69 patients with different B-cell malignancies. By combining standard clinical serological measurements with *in vitro* neutralization, flow cytometric phenotyping of immune cells and interferon gamma (IFNγ) ELISpot assays, the authors were able to provide detailed insights in the immune response to vaccination. In accordance with previous studies,[5,6] assessed by measurement of anti-spike IgG in serum, seroconversion rates were low with 27.1% and 46.8% following the first and second vaccines. In line with the previous study of Liebers et al.,[5] the anti-spike T-cell responses were not affected by specific B-cell malignancy treatment with a marked increase in response following the second dose. Interestingly, the incidence of virus-specific T-cell responses correlated with seroconversion after the first and second vaccine but not after the third and fourth once, suggesting that T- and B-cell responses are uncoupled at later time points. Remarkably, the authors identified a positive association post-fourth dose with neutralization titres and NK cell frequency. Thus, the size and quality of the antibody response was largely based on the function and presence of the B-lymphocyte population, whereas at later time points, when fewer seronegative patients were present, the number of NK cells was relevant.[4]

The study of Pinder et al.[4] demonstrates the value of repeated COVID-19 vaccination for patients with B-cell malignancies under B-cell depletion. Repeated dosing increases the B-cell response in these patients, thereby reducing the risk of severe COVID-19 and death as well as the risk of related complications. These data encourage patients with B-cell malignancies to take up repeated vaccination when offered. However, the study demonstrates as well that these patients remain vulnerable despite vaccination, which supports the routine use of antiviral agents such as nirmatelvir/ritonavir in this patient group.

Other factors had as well be found to be relevant to achieve sufficient anti-spike IgG antibody titres. Recently, we investigated 200 patients with hematologic malignancies, of those 96% with lymphoid neoplasms.[7] Seroconversion after the first booster vaccination was documented in 55% of patients. Higher age, lymphocytopenia, ongoing treatment and prior anti-CD20 B-cell depletion were independent predictors of booster failure. We could show that with each month between B-cell depletion and booster vaccination, the probability of seroconversion increased by approximately 4% ($p < 0.001$) and serum–antibody titre levels were significantly increasing, too. This finding supports the correlation between serologic response and COVID-19 vaccinations post-second dose observed in the study of Pinder et al.[4] Interestingly, B-cell depletion with obinutuzumab was associated with an 85% lower probability for seroconversion after prime-boost vaccination as compared to rituximab ($p = 0.002$) in our study.[7] This demonstrates that different compounds with anti-B-cell activity and potential of B-cell depletion may impact differently on the success of COVID-19 vaccination.

In conclusion, the work of Pinder et al.[4] gives further evidence to the concept that preventive and repetitive vaccination against SARS-CoV-2 remains essential for patients with B-cell malignancies under therapy. Due to protracted SARS-CoV-2 shedding, and due to the fact that part of patients with B-cell malignancies do not develop a sufficient immune response despite repeated vaccination, passive immunotherapy with monoclonal neutralizing antibodies directed against SARS-CoV-2 variants circulating at the time of infection and antiviral therapy, for example with remdesivir and nirmatrelvir/ritonavir, should be offered to these patients.[8] Finally, a combination of repeated vaccination and passive immunization in the case of SARS-CoV-2 infection will offer the highest safety level for patients with B-cell malignancies and B-cell depletion. Taken the above data together, the study of Pinder et al.[4] will be highly utile for physicians dealing with patients with B-cell malignancies under B-cell depleting treatment, as it underlines strongly the need for repetitive COVID-19 vaccination in this population, even in the case of previous failure to build up an adequate immune response.

AUTHOR CONTRIBUTIONS

All authors contributed to the design of the commentary. Ulrike Bacher and Evgenii Shumilov wrote the primary draft. Thomas Pabst reviewed the draft. The final version was approved by all authors.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

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

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REFERENCES

1. Bonuomo V, Ferrarini I, Dell'Eva M, Sbisà E, Krampera M, Visco C. COVID-19 (SARS-CoV-2 infection) in lymphoma patients: a review. World J Virol. 2021;10(6):312–25.
2. Nachar VR, Perissinotti AJ, Marini BL, Karimi YH, Phillips TJ. COVID-19 infection outcomes in patients receiving CD20 targeting T-cell engaging bispecific antibodies for B-cell non-Hodgkin lymphoma. Ann Hematol. 2023;1–3. https://doi.org/10.1007/s00277-023-05315-1
3. Defrancesco I, Ferretti VV, Morel P. SARS-CoV-2 infection in patients with Waldenström's macroglobulinemia: a multicenter international cohort study. Hemasphere. 2023;7(6):e887.
4. Pinder CL, Jankovic D, Fox TA, Kirkwood A, Enfield L, Alrubayyi A, et al. Humoral and cellular responses to SARS-CoV-2 in patients with B cell haematological malignancies improve with successive vaccination. Br J Haematol. 2023. https://doi.org/10.1111/bjh.18962

5. Liebers N, Speer C, Benning L, Bruch PM, Kraemer I, Meissner J, et al. Humoral and cellular responses after COVID-19 vaccination in anti-CD20-treated lymphoma patients. Blood. 2022;139(1):142–7.
6. Malard F, Gaugler B, Gozlan J, Bouquet L, Fofana D, Siblany L, et al. Weak immunogenicity of SARS-CoV-2 vaccine in patients with hematologic malignancies. Blood Cancer J. 2021;11(8):142.
7. Krekeler C, Reitnauer L, Bacher U, Khandanpour C, Steger L, Boeckel GR, et al. Efficacy of COVID-19 booster vaccines in patients with hematologic malignancies: experiences in a real-world scenario. Cancers. 2022;14(22):5512.
8. Luque-Paz D, Sesques P, Wallet F, Bachy E, Ader F, Lyon HEMINF Study Group. B-cell malignancies and COVID-19: a narrative review. Clin Microbiol Infect. 2023;29(3):332–7.

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