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COMMENTARY

Is COVID vaccine effective in patients with myeloid malignancy?

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, COVID-19) pandemic has challenged the clinical community in many aspects. One of the major issues is the outcome and optimal approach to patients with impaired immune system due to an underlying disorder and/or its treatment. The case of patients with cancer and haematological neoplasms is an example. Studies conducted in unvaccinated patients with haematological neoplasms reported poor outcome of COVID infections, with up to 34% in -hospital mortality.[1]

The introduction of COVID vaccination has been shown to be effective in preventing infection in the general population,[2,3] as well as attenuating the disease intensity and complications in the real world.[4] However, since patients with haematological neoplasms were excluded from these studies, their outcome, even if vaccinated, remains unclear. Can COVID vaccine prevent infection or attenuate it in this patient population?

Several reports have suggested diminished seroconversion rate and reduced anti-S-antibody (Ab) titers in haematological patients, compared with healthy controls, following COVID vaccine. These reports focused on patients with lymphoid neoplasms, especially CLL,[5,6] lymphomas[7,8] and multiple myeloma.[9–11] Patients under active treatment, especially B-cell depleting agents, such as rituximab, were more vulnerable.[5,7,9]

These reports raised several questions: What is the correlation between the post vaccine humoral response and the whole anti-COVID immunity? What does it mean about the other components of the immune system? How can anti-COVID humoral response be translated into clinical outcomes? Does it correlate with the disease clinical manifestations? And finally, what happens to patients with myeloid disorders?

We have recently reported that patients with various haematological neoplasms (n = 32 516), despite COVID vaccination and compared with vaccinated (×2) healthy controls suffer more from COVID clinical outcomes: higher infection rate (proven by PCR), more symptoms and hospitalizations, more severe disease, and higher rate of mortality.[12] Patients with lymphoma and myeloma on active treatment, suffered more from COVID infection and complications compared with untreated patients. The relatively small number of clinical events (COVID infection rates and complications) in patients with myeloid diseases, did not allow drawing conclusions regarding the effect of COVID vaccination in this patient population.

A partial answer to the question of the outcome in patients with myeloid neoplasms is provided in this issue of the British Journal of Haematology.[13] Dr. Akio Mori and colleagues from Japan, report their experience with the humoral response to COVID vaccination in patients with myeloid disorders. They evaluated the humoral response to an mRNA-based COVID-19 vaccine in 69 patients, 46 with acute myeloid leukaemia (AML), and 23 with myelodysplastic syndromes (MDS). The endpoints were the seroconversion rate and the serum anti-spike SARS-Cov-2 Ab titers, measured 3 months following the second vaccine dose. The results were compared to healthy controls. Seroconversion rates for AML and MDS were 94.7% and 100%, respectively, similar to healthy population. AML patients, especially those in complete remission (CR) and treatment-free, demonstrated similar Ab titers to healthy controls, and higher titers than MDS patients. The authors concluded that patients with myeloid malignancies appear to be more responsive than patients with lymphoid malignancies to vaccines. Given the small number of evaluated patients one should be cautious in proceeding with further and subgroup analysis, including predisposing factors and the influence of duration from diagnosis on the Ab titre.

This report, despite its limitations, delivers an important message to the clinical community: The humoral response

of patients with AML and MDS to the mRNA-based COVID vaccine appears to be satisfactory. This is in contrast with the findings in lymphoid malignancies on reduced humoral response in these patients. This conclusion is supported by a recent publication.[14]

However, one should be aware of the limitations of the study and the questions that still remain open, thus, requiring caution before applying the conclusions into clinical practice. The numbers studied was small. Moreover, the studied population was heterogeneous, including patients with MDS of all types, AML, some of them in CR, some receiving maintenance treatment. The studied population was lacking a significant group of patients with myeloid disorders – those with myeloproliferative neoplasms. Also, one should take into consideration that the healthy controls in this study were not the ideal control population: a small number (n = 43) of health workers with a median age of 56 years (50–72), and female predominance (69.8%). It is also important to note that we still do not know the minimal requirements for intact humoral anti-COVID protection.

It should be emphasized that only the humoral response was tested in this study. Other components of the immune system, macrophages, antigen-presenting cells and T-cells were not analysed. In fact, little has been reported so far on the T-cell function in COVID. A few reports suggested T-cell dysfunction in infected cancer patients.[15] In healthy individuals, a direct correlation between seroconversion and T-cell response to COVID vaccine has been shown.[16] But, what is the case with haematological patients? What about their T-cell response after vaccination? Emerging reports suggest that despite lower than normal seroconversion rate in patients with lymphoid neoplasms, although these patients experience an impaired T-cell function, they still benefit from some degree of T-cell protection.[17,18] Two recent reports suggested that the post vaccine COVID T-cell immunity although inferior to healthy controls, and regardless of the low seroconversion rate might still confer anti-COVID protection in patients with lymphoma[19] and myeloma.[20] However, as mentioned in the accompanying commentary,[21] we look forward to results from ongoing trials of COVID-19 vaccinations in immunocompromised patients (NCT 04895982, OCTAVE-DUO, BMT-CTN 2101 trial, etc.), which might provide more accurate answers to this important question. If this T-cell protection can be extended to myeloid diseases, it might be of great advantage to these patients.

Finally, there is still a gap between the function of the immune system, both the humoral and cellular components, and real life clinical manifestations.[4,12]

Despite the study's pitfalls, and the remaining open questions, Mori and colleagues teach us an important lesson—patients with myeloid disorders, especially those in CR and treatment-free appear to have satisfactory humoral response to COVID vaccine. The role of treatment remains open. Future research will have to clarify whether the lower humoral response in treated patients is due to the disease status or related to treatment itself.[12] Thus, while patients with lymphoid malignancies are still vulnerable to COVID manifestations and complications despite vaccination, and strategies, such as a third vaccine dose, in an attempt to improve their ability to cope with the disease are ongoing, perhaps patients with myeloid neoplasms are more protected. If these data are confirmed in larger and additional studies and can also be translated into clinical outcomes, it might deliver good news to the clinical community and patients with myeloid neoplasms.

Highlights/Key points

The introduction of mass COVID vaccination has been successfully applied for the general population in many countries. However, patients with impaired immune system, such as those with haematological neoplasms, were excluded from the vaccine trials. Emerging data suggest that patients with lymphoid neoplasms are incapable of mounting an adequate post vaccine anti-COVID humoral response. The question of the outcome of vaccinated patients with myeloid malignancies has gained little attention. Dr. Akio Mori and colleagues provide a partial answer to that question: They report that patients with AML and MDS have high rate of seroconversion like normal controls. Also, untreated AML patients in CR produce anti-S Ab titers like normal controls.

REFERENCES

1. Vijenthira A, Gong IY, Fox TA, Booth S, Cook G, Fattizzo B, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. Blood. 2020;136:2881–92.
2. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384:403–16.
3. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med. 2020;383:2603–15.
4. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 vaccine in a Nationwide mass vaccination setting. N Engl J Med. 2021;384:1412–23.
5. Herishanu Y, Avivi I, Aharon A, Shefer G, Levi S, Bronstein Y, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood. 2021;137:3165–73.
6. Benjamini O, Rokach L, Itchaki G, Braester A, Shvidel L, Goldschmidt N, et al. Safety and efficacy of BNT162b mRNA Covid19 vaccine in patients with chronic lymphocytic leukemia. Haematologica. 2022;107(3):625–34.
7. Perry C, Luttwak E, Balaban R, Shefer G, Morales MM, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with B-cell non-Hodgkin lymphoma. Blood Adv. 2021;5:3053–61.
8. Gurion R, Rozovski U, Itchaki G, Gafter-Gvili A, Leibovitch C, Raanani P, et al. Humoral serologic response to the BNT162b2 vaccine is abrogated in lymphoma patients within the first 12 months following treatment with anti-CD2O antibodies. Haematologica. 2022;107(3):715–20.
9. Avivi I, Balaban R, Shragai T, Sheffer G, Morales M, Aharon A, et al. Humoral response rate and predictors of response to BNT162b2 mRNA COVID19 vaccine in patients with multiple myeloma. Br J Haematol. 2021;195:186–93.

10. Terpos E, Trougakos IP, Gavriatopoulou M, Papassotiriou I, Sklirou AD, Ntanasis-Stathopoulos I, et al. Low neutralizing antibody responses against SARS-CoV-2 in older patients with myeloma after the first BNT162b2 vaccine dose. Blood. 2021;137(26):3674–6.
11. van Oekelen O, Gleason CR, Agte S, Srivastava K, Beach KF, Aleman A, et al. Highly variable SARS-CoV-2 spike antibody responses to two doses of COVID-19 RNA vaccination in patients with multiple myeloma. Cancer Cell. 2021;39:1028–30.
12. Mittelman M, Magen O, Barda N, et al. Effectiveness of the BNT162b2mRNA Covid-19 vaccine in patients with hematological neoplasms. Blood2022. doi: https://doi.org/10.1182/blood.2021013768 [published online ahead of print 18 October 2021].
13. Mori A, Onozawa M, Tsukamoto S, Ishio T, Yokoyama E, Izumiyama K, Saito M, Muraki H, Morioka M, Teshima T, Kondo T Humoral response to mRNA-based COVID-19 vaccine in patients with myeloid malignancies. Br J Haematol 2022;197:691–696.
14. Petzer V, Steiner N, Angelova-Unterberger O, et al. Serologic responses to COVID-19 vaccines in hematological patients are predominantly impaired in lymphoid but not in myeloid malignancies. Hema. 2022;6(3):e686.
15. Ehmsen S, Asmussen A, Jeppesen SS, et al. Antibody and T cell immune responses following mRNA COVID-19 vaccination in patients with cancer. Cancer Cell 2021;39(8):1034–1036. 23.
16. Sahin U, Muik A, Vogler I, Derhovanessian E, Kranz LM, Vormehr M, et al. BNT162b2 vaccine induces neutralizing antibodies and polyspecific T cells in humans. Nature. 2021;595(7868):572–7.
17. Bonifacius A, Tischer-Zimmermann S, Dragon AC, Gussarow D, Vogel A, Krettek U, et al. COVID-19 immune signatures reveal stable antiviral T cell function despite declining humoral responses. Immunity. 2021;54:340–54.e6.
18. Moor MB, Suter-Riniker F, Horn MP. Humoral and cellular responses to mRNA vaccines against SARS-CoV-2 in patients with a history of CD20 B-cell depleting therapy (RituxiVac): an investigator-initiated, single-Centre, open-label study. Lancet Rheumatol. 2021;3:e789–97.
19. 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.
20. Enßle JC, Campe J, Schwenger A, Wiercinska E, Hellstern H, Dürrwald R, et al. Severe impairment of T-cell responses to BNT162b2 immunization in patients with multiple myeloma [letter]. Blood. 2021;139(1):137–42.
21. Hill LC, Lulla PD. COVID-specific T's may offset therapeutically endangered B's. Blood. 2022;139(1):12–3.

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