COVID-19

A needed boost against COVID-19 in lymphoma

Patients with cancer are known to be at increased risk of infection and severe complications from COVID-19, with vaccination being key for their protection. A prospective study now evaluates the effect of vaccination against COVID-19 on the immune response mounted by patients with lymphoma.

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As the COVID-19 pandemic continues, understanding the nature of the causative virus and how it affects the body remains an utmost priority. Several studies have shown that patients who have cancer are at increased risk of being infected with SARS-CoV-2 and that they tend to suffer a more severe form of the disease when infected, with increased risk of death[1–4]. Specifically, patients with hematological malignancies were found to have increased risk of a more severe course of COVID-19 when compared to patients with solid tumor malignancies[5].

With the advent of COVID-19 vaccination, significant effort has been made to determine the efficacy of the vaccine in patients with malignancies. High rates of seroconversion have been observed generally, with positive anti-spike antibodies following full vaccination against COVID-19 (ref. [6]). Higher seroconversion rates were seen predominantly in patients with solid tumor malignancies, compared with those who have hematological malignancies. The rates of seroconversion were even lower in subsets of patients with blood cancer — including lymphoid malignancies — who received specific therapies, such as anti-CD20 antibody therapy, stem-cell transplantation, Bruton's tyrosine kinase (BTK) inhibitors and chimeric antigen receptor–T cell (CAR-T) therapy[6–8].

Subsequent work demonstrated waning responses to the initial COVID-19 vaccination series[9], leading to the conclusion that booster vaccinations were necessary to provide ongoing immunity to COVID-19 in the general population. Recent data from patients with cancer showed that booster doses of COVID-19 vaccines led to substantial seroconversion in those patients who remained negative after initial vaccination[10]. The patients who did not demonstrate seroconversion appeared to be in the subset with lymphoid neoplasms, particularly those on anti-B-cell-directed therapies[10]. In this issue of *Nature Cancer*, Lim et al.[11] add to these findings by reporting an evaluation of the dynamics of the immune response in patients with B cell malignancies who have received the initial vaccination series as well as booster vaccination against COVID-19.

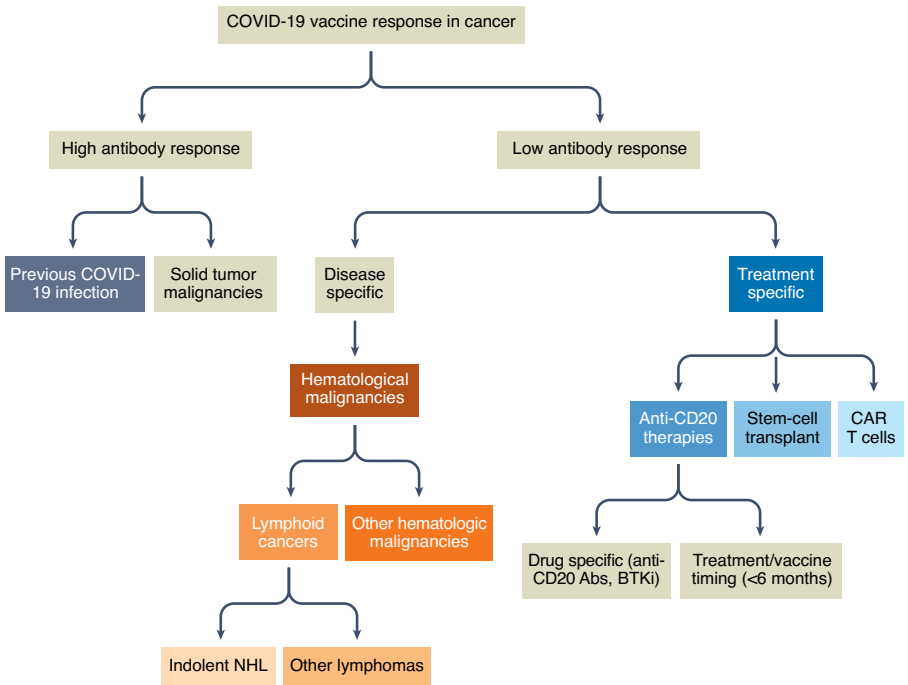

Fig. 1 | Immune response to COVID-19 vaccination in patients with cancer. Previous COVID-19 infection, as well as the presence of solid tumors, leads to a higher antibody response to vaccination than the presence of hematological malignancies. Within hematological malignancies, and particularly lymphoma, patients with indolent NHL tend to have a lower response than other lymphoma subtypes. Treatment-specific etiologies of decreased vaccine response include CAR-T therapy, stem-cell transplantation and anti-CD20 antibody therapy. This can be further broken down into drug-specific etiologies, as well as etiologies due to timing between therapy and vaccination. Abs, antibodies; BTKi, BTK inhibitor.

The authors conducted a UK-based prospective multicenter observational study to assess the immune response to COVID-19 vaccination in patients with lymphoma who received the adenovirus-based ChAdOx1 nCoV-19 115 (ChAdOx1) vaccine or the mRNA BNT162b2 vaccine. Patients who tested positive for anti-nucleocapsid antibodies, indicating previous infection, were excluded. Participating patients had been diagnosed with lymphomas, including Hodgkin lymphoma (HL), aggressive and indolent non-Hodgkin lymphoma (NHL), and peripheral T cell/natural killer (NK) lymphoma (PTCL) (Fig. 1).

The authors noted that patients in the 'on treatment' group (defined as receiving the first vaccine within 24 weeks of completing lymphoma-directed therapy or initiating lymphoma therapy within 4 weeks after the first vaccine), had significantly impaired antibody responses compared to those patients not receiving treatment. This effect was even more striking when evaluated by

lymphoma subtype: in the on-treatment group, roughly 11% of patients with HL had undetectable antibody levels, compared to more than 50% of patients with aggressive or indolent NHL. This effect was substantially less evident in the 'no treatment' group. Reduced levels of anti-S antibodies were detected in patients with indolent NHL compared to other lymphoma subtypes, regardless of treatment history. These data show a treatment-related (such as recent lymphoma-directed therapy) effect on the patient's ability to maintain an immune response, as well as disease-specific intrinsic immune dysfunction (as seen in indolent NHL), which both impair the ability to produce sufficient antibody levels. When assessing antigen-specific T cell responses, the authors observed no differences related to treatment status, but noted variability within disease subtypes. Specifically, in indolent NHL, there was an inferior cellular response in patients not on treatment, compared to those on treatment.

Next, Lim et al.[11] evaluated therapy-related differences in the patients' immune responses. To assess the influence of anti-CD20 therapy on the immune response without the possible confounding effect of disease-related immune impairment, they selected a cohort of patients with aggressive B cell NHL. They found that 50% or more of patients did not have detectable antibodies if they received their first vaccine dose while on, or within 6 months of, anti-CD20 antibody therapy. This percentage decreased with time from therapy and ultimately all patients who were vaccinated more than 12 months after anti-CD20 antibody therapy had detectable antibody levels. The authors hypothesized that the impaired immune response while on anti-CD20 antibody therapy was due to decreased B cell levels, and confirmed that differences in B cell counts positively correlated with changes in antibody titers.

To evaluate the effect of chemotherapy on the immune response in the absence of anti-CD20 antibody therapy, Lim et al.[11] assessed patients with HL independently. Patients vaccinated shortly before or during chemotherapy had lower antibody levels, compared to patients vaccinated after completion of chemotherapy. Additionally, cellular responses in patients with HL appeared to be preserved regardless of chemotherapy status. Cellular responses to therapy were also assessed in patients who received bendamustine — a drug known to reduce peripheral blood T cell levels. Neither previous bendamustine use nor the patient's serological response to vaccination correlated with T cell levels. However, it should be noted that the researchers did find a higher cellular response in patients who received the ChAdOx1 vaccine compared to the BNT162b2 vaccine, although the clinical significance of this remains uncertain. Autologous stem-cell transplantation also negatively impacted antibody response, as patients who were vaccinated 3 weeks before, or up to 5 months after, transplantation had decreased antibody response compared to those who were vaccinated 12 months after transplant.

Finally, the authors evaluated the response to a third dose of COVID-19 vaccination and found that it correlated with timing between lymphoma treatment and the third vaccine dose, as well as the specific treatment itself. Only 17% of those patients with lymphoma who received the third vaccine dose within 1 year of anti-CD20 antibody therapy had an antibody response, compared to 75% of patients with indolent NHL on BTK inhibitors or venetoclax, and 100% of patients with HL on chemotherapy. In addition, treatment-naive patients or those who received a third vaccination more than 24 weeks after lymphoma therapy had improved antibody levels compared to those without delayed vaccination. Importantly, 50% of patients who did not have a T cell response after the second vaccine did have a response after the third dose.

The present study reports several important findings for patients with lymphoma. Chief among them is that the type of treatment that a patient receives can affect their ability to mount an immune response. This was primarily noted as an extended decreased immune response in patients who received anti-CD20 antibody therapy. However, T cell responses were preserved regardless of the patient's treatment status, which may offer protection in the absence of high immunoglobulin-G levels, as also seen in other studies[12]. A more noteworthy insight was that the timing of therapy in relation to vaccination was key in determining the immune response to the vaccine. Patients vaccinated within 6 months of therapy had a lower likelihood of achieving a response to vaccination and this effect persisted through the third vaccine dose[11]. This consideration may have a role in vaccination timing and treatment decisions for patients with cancer, especially those on maintenance therapy with anti-CD20 antibodies. In addition, the present work also noted disease-specific differences, primarily as related to indolent NHL. In that patient cohort, the authors noted both decreased anti-S antibody levels and decreased T cell responses. Decreased T cell function was previously reported in indolent lymphomas, such as follicular lymphoma[13], and so this latter finding was not unexpected. When evaluating the third vaccine dose, most patients participating in the current study were found to have an increased antibody response to the vaccine regardless of lymphoma subtype, suggesting a general benefit of repeated vaccination in patients with lymphoma. This excludes patients treated with anti-CD20 antibody therapy within one year of vaccination, as they generally did not respond to a third vaccine.

There are several limitations to this study as noted by the authors, such as its observational nature. However, it has merit in light of the large cohort of patients evaluated. It will be interesting to see further research in other subtypes of hematological malignancies and compare those data to the findings presented here. Moreover, by furthering our understanding of the effects of multiple COVID-19 vaccinations on patients with lymphoma and patients on different cancer-directed treatment regimens, the article of Lim et al. will aid in the management of these patients.

More than two years into the COVID-19 pandemic, the ever-increasing knowledge on COVID-19 and vaccine responses is being counterbalanced by the evolution of the virus, and the biomedical urgency to protect vulnerable populations persists. Further work of this type will be needed to provide the best prophylactic and therapeutic approaches to patients with hematological malignancies. ❐

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Competing interests

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