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by Caroline Besson

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It is time to adapt anti-CD20 administration schedule to allow efficient anti-SARS-CoV-2 vaccination in patients with lymphoid malignancies.

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Patients with comorbidities are especially sensitive to coronavirus disease 2019 (Covid-19). This is notably true for patients with cancer including patients with a recent (<5 years) diagnosis of haematological malignancies who have a ≥2.5-fold increased risk of death from Covid-191. Patients with non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL) share immune-deficiencies due to the biological features of NHL/CLL per se (hypogammaglobulinemia, frequent neutropenia, lymphopenia or lymphocytic dysfunction) and to their treatments (chemotherapy, anti-CD20 monoclonal antibodies (anti-CD20), Bruton tyrosine kinase inhibitors (BTKi) or Bcl2 inhibitors (Bcl2i)), leading to increased incidence and severity of infections. NHL/CLL patients are more likely to develop severe2 and/or prolonged forms of Covid-193. The Covid-19-related mortality of NHL patients was shown to increase with age, relapsed/refractory disease and administration of anti-CD20 therapy within one year3 while it was shown to be related to age, comorbidities but not with therapy (mainly BTKi) among CLL patients4. Therefore, these populations deserve particularly to be protected against Covid-19.

Vaccination against SARS-CoV-2 was shown to prevent Covid-19 in the general population. The efficacy of vaccination in CLL/NHL population requires further evaluation as immunocompromised patients were excluded from initial studies of SARS-CoV-2 mRNA vaccines. Only limited data reporting the efficacy of vaccination in these populations have been published. Herishanu et al5 studied 167 CLL patients from a single center and reported that their antibody response to the BNT162b2 mRNA COVID-19 vaccine was affected by disease activity and by treatments. It decreased from 55.2% in treatment-naive patients to 16.0% in patients on treatment at the time of vaccination. Remarkably, none of the 22 patients exposed to anti-CD20 within less than 12 months before vaccination had an antibody response5. This raises particular concerns with these drugs.

In this issue of the Journal, Benjamini et al report on a larger multicentric series of 373 CLL patients followed across 9 Israeli medical centers, that received two doses of BNT162b2 mRNA Covid-19 vaccine6. Consistently with Herishani’s study5, 61% of the treatment-naive patients had a serological response to vaccine, versus 23% and 24% among patients on
BTKi or BCL2i, and only 5% of patients who received anti-CD20 antibodies during the year before vaccination. Deepening the analysis to clinical and biological factors, they demonstrate that age < 70 years, normal IgM (>=40 mg/dL), IgA (>=80 mg/dL) and IgG (>=700 mg/dL) levels, normal haemoglobin level (>=13.5 g/dL for males or >= 12 g/dL for females) are associated with an antibody response. This allowed the construction of a specific score that predicted response to vaccine. In the same issue, Gurion et al, analyzed the antibody response after vaccination with two doses of BNT162b2 mRNA Covid-19 vaccine of 162 patients with lymphoma enrolled in two medical centers in Israel7. Positive serological responses were observed in 51% of the patients. In a multivariate analysis, active lymphoma and anti-CD20 administration within one year before the second vaccine dose were identified as negative predictors for antibody response. Interestingly, the rate of seropositivity increased according to the time between anti-CD20 administration and vaccine, from 3% within 45 days, to 22% between 45 days and one year and to 80% after one year. Remarkably, the latter percentage was equal to that of patients never exposed to anti-CD20.

The lack of robust data from large and pluri-centric cohorts available so far in these high-risk populations renders the present studies of the utmost importance for physicians taking care of NHL/CLL worldwide. Two important messages can be drawn from the results reported by these studies. First, patients with NHL/CLL frequently fail to develop effective humoral response to BNT162b2 vaccine. The striking observation that recent anti-CD20 therapy strongly impairs the development of antibody response after vaccination should be at the forefront of concerns. The second major information is the identification of other risk factors associated with lack of humoral response in this setting. Besides older age, risk factor for lack of antibody response that has already been identified in the general population, some NHL/CLL-specific factors also seem to impact serologic response such as active disease, and, among CLL patients only, lower hemoglobin and/or immunoglobulin levels. The usefulness of the CLL score built with these factors needs to be determined in clinical practice.

The two studies suffer from significant limitations, mostly related to the short follow-up after vaccination (2-6 weeks and 2-3 weeks after the 2nd vaccine dose in patients with NHL and CLL respectively). With longer follow-up, it will be especially important to have data on Covid-19 occurrence after vaccination in these cohorts of patients. As B-cell depletion may also affect the generation of both B and T-cell memory responses8, the serological data should be supplemented by the exploration of T-cell immune responses. Indeed, T-cell immunity has a major role in generating durable protective immunity after viral vaccination. Recent reports, performed among non-immunocompromised patients, show that two doses of BNT162b1 can elicit robust CD4+ and CD8+ T cell responses9. Although the evaluation of T-cell responses
is not as robust and reproducible as serological responses, T-cell responses should be evaluated in naive CLL/NHL patients as well as among those receiving BTKi, Bcl2i, chemotherapy and/or anti-CD20 to establish whether it could provide additional protection.

Overall, these findings raise questions about the management of patients with CLL/NHL during this Covid-19 era, for whom there are currently no consensual guidelines. It is time to consider adapting our therapeutic strategies in CLL/NHL patients. First, in any non-critical clinical situation, SARS-CoV-2 vaccination should be proposed before the onset of treatments with BTKi, Bcl2i or anti-CD20. Secondly, to prevent prolonged Covid-19 and lack of vaccination efficacy, avoiding or delaying the administration of anti-CD20 monoclonal antibodies may be considered in patients with indolent NHL/CLL with i) low tumor burden and mild symptoms or cytopenia, for which delaying the initiation of the treatment will not place the patient at risk, or ii) consider avoiding to repeat the use anti-CD20 in patients with NHL in the relapse/refractory setting when other reasonable options are available. Moreover, as already adopted in many centers, avoidance or suspension of maintenance therapy with anti-CD20 in patients with indolent B-cell lymphoma in complete remission to allow their vaccination should also be recommended. This decision should not preclude the patient from receiving the most efficacious treatment strategy and requires consideration of the disease characteristics and the patient's history.

Lastly, systematic vaccination of their proxies and hospital workers should also benefit directly to patients. Other vaccination strategies should also be explored in these patients such as the effect of a third vaccine dose in nonresponding patients or in those with a low serological response. This approach is currently recommended in some countries like France although its efficacy is not demonstrated. Additional large studies are required to address the question of vaccination in cancer patients such that supported by the “Covid-19 and Cancer Global Taskforce”\textsuperscript{10} and, more specifically among vaccinated CLL/NHL patients, to specify the level of cellular protection against infection and to determine the risk of clinical Covid-19 and its severity. Meanwhile, individuals with CLL/NHL should receive the Covid-19 vaccine, be informed that they are unlikely to be protected and continue social distancing and adhere to other proven mitigation strategies such as mask wearing. Finally, these findings should contribute to the elaboration of guidelines for the management of NHL/CLL patients during the Covid-19 pandemic. This would be a necessary and essential step towards the improvement of the efficiency of vaccination in this setting.

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