It is time to adapt anti-CD20 administration schedules 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 a hematologic malignancy who have a ≥2.5-fold increased risk of death from COVID-19.[1] Patients with non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL) share immune-system 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 [BTK] inhibitors or BCL2 inhibitors), leading to an increased incidence and severity of infections. NHL/CLL patients are more likely to develop severe[2] and/or prolonged forms of COVID-19.[3] The COVID-19-related mortality of NHL patients was shown to increase with age, relapsed/refractory disease and administration of anti-CD20 therapy within 1 year[3] while it was shown to be related to age, comorbidities but not with therapy (mainly BTK inhibitors) among CLL patients.[4] Therefore, these populations need to be particularly protected against COVID-19.

Vaccination against severe acquired respiratory syndrome coronavirus 2 (SARS-CoV-2) was shown to prevent COVID-19 in the general population. The efficacy of vaccination in the NHL/CLL population requires further evaluation as immunocompromised patients were excluded from initial studies of SARS-CoV-2 mRNA vaccines. Only limited data on the efficacy of vaccination in these populations have been published. Herishanu *et al.*[5] 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 response.[5] This raises particular concerns about these drugs.

In this issue of *Haematologica*, Benjamini *et al.* report on a larger multicenter series of 373 CLL patients, followed in nine Israeli medical centers, who received two doses of BNT162b2 mRNA COVID-19 vaccine.[6] Consistently with the study by Herishani *et al.*,[5] 61% of the treatment-naive patients had a serological response to vaccine, compared to 23% and 24% among patients on BTK inhibitors or BCL2 inhibitors, and only 5% among 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 hemoglobin 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 vaccination.

In the same issue, Gurion *et al.*, analyze 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 Israel.[7] Positive serological responses were observed in 51% of the patients. In a multivariate analysis, active lymphoma and administration of anti-CD20 treatment within 1 year before the second dose of vaccine were identified as negative predictors for antibody response. Interestingly, the rate of seropositivity increased according to the time between anti-CD20 administration and vaccination, from 3% within 45 days, to 22% between 45 days and 1 year and to 80% if the vaccine was given more than 1 year after anti-CD20. Remarkably, the last percentage was equal to that of patients never exposed to anti-CD20.

The lack of robust data from large and multicenter cohorts available so far in these high-risk populations renders the present studies of the upmost importance for physicians taking care of NHL/CLL patients worldwide. Two important messages can be drawn from the results reported by these studies. First, patients with NHL/CLL frequently fail to develop an 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, a risk factor for lack of antibody response, which had already been identified in the general population, some NHL/CLL-specific factors also seem to affect serological 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 second dose of vaccine in patients with NHL and CLL, respectively). With longer follow-up, it will be especially important to obtain data on the occurrence of COVID-19 after vaccination in these cohorts of patients. As B-cell depletion may also affect the generation of both B- and T-cell memory responses,[8] 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 studies, performed among non-immunocompromised patients, show that two doses of BNT162b1 can elicit solid $CD4^+$ and $CD8^+$ T-cell responses.[9] Although the evaluation of T-cell

responses is not as robust and reproducible as serological responses, T-cell responses should be evaluated in treatment-naïve NHL/CLL patients as well as among those receiving BTK inhibitors, BCL2 inhibitors, chemotherapy and/or anti-CD20 to establish whether it could provide additional protection.

Overall, the findings raise questions about the management of patients with NHL/CLL during this COVID-19 era, for whom there are currently no consensual guidelines. It is time to consider adapting our therapeutic strategies in these patients. First, in any non-critical clinical situation, SARS-CoV-2 vaccination should be proposed before the onset of treatments with BTK inhibitors, BCL2 inhibitors or anti-CD20. Secondly, to prevent prolonged COVID-19 and lack of vaccination efficacy, avoiding or delaying the administration of anti-CD20 may be considered in patients with indolent NHL/CLL with low tumor burden and mild symptoms or cytopenia, for whom delaying the initiation of the treatment will not place the patient at risk. Furthermore, consideration should be given to not re-administering 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 a patient from receiving the most efficacious treatment strategy and requires consideration of the disease characteristics and the patient's history.

Lastly, systematic vaccination of the patients' relatives and close associates and hospital workers should also benefit the patients directly. 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, for example France, although its efficacy has not yet been demonstrated. Additional large studies are required to address the question of vaccination in cancer patients, such as that supported by the "COVID-19 and Cancer Global Taskforce"[10] and, more specifically, among vaccinated NHL/CLL 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 NHL/CLL 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 production of guidelines for the management of NHL/CLL patients during the COVID-19 pandemic, an essential step towards improving the efficiency of vaccination in this setting.

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