










REVIEW



Spanish Society of Hematology and Hemotherapy expert consensus opinion for SARS-CoV-2 vaccination in onco-hematological patients

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ABSTRACT

In the midst of the COVID-19 pandemic, different vaccines in front of SARS-CoV-2 have been approved and administered in different vulnerable populations. As patients with cancer were excluded from pivotal trials of vaccination, little is known on their immunogenic response to these vaccines, particularly in patients with severely impaired immune system. In response to that uncertainty, the Spanish Society of Hematology and Hemotherapy launched an initiative aimed to provide recommendations for vaccination of the main hematological conditions. This document is based on the available information on COVID-19 outcomes, prior knowledge on vaccination in hematological patients, recent published data on serological response in onco-hematological patients and expert opinions. New information about SARS-CoV-2 vaccination will be gathered in the near future, providing new scientific grounds to delineate the most adequate management of vaccination in patients with hematological diseases. The current limited data on SARS-CoV-2 vaccines in hematological patients represents a major limitation of this expert consensus opinion. In fact, the speed in which this field evolves may reduce their validity in the near future.

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Introduction

Data on SARS-CoV-2 disease (COVID-19) in patients with cancer have shown an exceeding associated mortality compared to general population [1–3], particularly in onco-hematological patients where overall mortality rates range from 20% to 40% [4–7]. Concurrent critical conditions in this population

include advanced age, associated comorbidities, impaired performance status, neutropenia, active disease, active treatment with monoclonal antibodies (mAbs), and those diagnosed with acute myeloblastic leukemia (AML) or lymphoproliferative neoplasms [4–7]. Furthermore, onco-hematological patients and stem-cell transplantation (SCT) recipients are

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characterized by a long duration of SARS-CoV-2 excretion with a potential long-lasting infectivity [8]. Overall, these facts support the prioritization of SARS-CoV-2 vaccination in patients with onco-hematological diseases [9].

As part of the response to the COVID-19 pandemic, there is a rapid roll-out and approval of SARS-CoV-2 vaccines [1,9,10], with more than 180 SARS-CoV-2 vaccines currently under development [11]. Efficacy data in general population are encouraging, with the mRNA-based vaccines reporting more than 90% protection from COVID-19 with good safety profile [12,13], although the durability of protection, and thus the need for repeated vaccinations, remains to be ascertained. Unfortunately, clinical trials of SARS-CoV-2 vaccination excluded cancer patients receiving anti-cancer therapy or taking immunosuppressive drugs. Therefore, reliable data on the effectiveness of such vaccines in onco-hematological and immunosuppressed patients are scarce and based on prospective observational studies [14–20], making difficult the elaboration of precise evidence-based vaccination recommendations and emphasizing the urgent need for prospective studies to address vaccine efficacy in this population.

Onco-hematological diseases differ widely in their characteristics, treatments, degree of humoral and cellular immunosuppression, and in the risk of infectious-related morbidity and mortality. For this reason, it is necessary to develop individualized recommendations [21–25] for each group of disease/procedures considering the disease type and remission status, the class of treatment as well as the most appropriate timing for vaccination. Serological determinations in patients with blood cancer vaccinated against several pathogens show highly variable responses (from 0% to 85%) after vaccination, depending on the disease and the time of administration [26,27]. Of note, efficacy could be enhanced by revaccinating at the end of the disease treatment or with high-dose vaccine or selecting the timing of vaccination according to the state of the disease [28,29]. Finally, the immunosuppression associated to the onco-hematological processes makes unsuitable the use of live attenuated vaccines with replicating virus (LARV), owing to the risk of inducing disease [30].

Many general recommendations for vaccination have been elaborated by scientific societies [1,31–34], although they did not include specific recommendations considering the different types of disease and/or procedures. With the current areas of uncertainty on the efficacy of SARS-CoV-2 vaccines in this vulnerable

population, the SEHH elaborated disease-specific recommendations of vaccination based on the risk of severe COVID-19 outcome, the likelihood of serological response reported with other vaccines, and both the disease and the treatment status.

Methodology

On January 2021, the SEHH designated a panel composed by experts in different diseases/procedures along with infectious diseases and microbiologist specialists. The goal was to provide an expert opinion consensus for SARS-CoV-2 vaccination in order to maximize the serological response and safety. The panel used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach [35,36] to assess the certainty in the evidence. However, we decided not to grade our recommendations due to the lack of clinical trials with SARS-CoV-2 vaccines in hematological patients at the time of writing this document. The observational studies currently available in this setting [14–20] were also critically reviewed and taken into consideration to reach a final consensus among the expert panel. Prior studies and guidelines on vaccination against different pathogens [21–25], along with the optimal time of immunization in onco-hematological patients were analyzed. In addition, current available information on serological responses after SARS-CoV-2 vaccines in hematological patients as well as recommendations for SARS-CoV-2 vaccination provided by different international scientific groups were critically reviewed [1,31–34]. Furthermore, the current knowledge on risk factors for severe COVID-19 on each onco-hematological disease/procedure were specifically analyzed.

This expert consensus opinion document is aimed at providing to the hematological community a practical tool for decision-making and for patient counseling. This consensus is based on current knowledge in other vaccine-preventable infectious diseases along with the scarce data currently available regarding SARS-CoV-2 vaccines in hematological patients (Table 1).

General considerations concerning SARS-CoV-2 vaccination

The expert panel considered variables that could anticipate the likelihood to elicit a protective serological response after SARS-CoV-2 vaccine. In addition, prevaccination serologies against SARS-CoV-2 may identify prior contact, suggesting the possibility of boosting serological response. After vaccination, the

antibody response monitoring could have several advantages in immunocompromised patients; first, physicians can easily identify poor responders. Secondly, the identification of poor responders could be beneficial in the future selection of candidates to receive booster doses or revaccination at a later time point. Third, in case of SARS-CoV-2 breakthrough infections in vaccinated patients, the availability of prior serological tests could be used to correlate antibody response and clinical protection. Last but not least, there is an urgent need to evaluate the durability of antibody response in these patients. Ideally, monitoring should be performed only in those who are at risk of poor response, although there is scarce data on predictive factors for antibody response in all onco-hematological patients. Currently and according to the available information, we suggest to focus antibody monitoring especially but not limited to CLL patients, those who received anti-CD20 mAb in the last 12 months, in NHL and MM patients and in ASCT, allo-HSCT and CAR-T cell recipients. It should be noted that appropriate tests specific for the SARS-CoV-2 particles used in the vaccination should be used. In addition, it is advisable to assess seroconversion using standardized serological ELISA or chemiluminescence immunoassay techniques, although these tests are semi-quantitative and correlate moderate to highly with serum neutralizing antibody titers [37]. In vaccinated individuals with suspected SARS-CoV-2 re-infection, apart from PCR, serological test should include IgM/IgG against the nucleocapsid protein (N).

Various scientific societies have developed vaccination recommendations for patients with cancer, immunosuppressed, and SCT recipients [1,31–34]. These recommendations are based on preliminary data without specific information on the response to SARS-CoV-2 vaccine in these patients. Unfortunately, they lack specific recommendations for each of the hematological malignancies and/or procedures. The American Society of Hematology (ASH) guide [34] and the European Hematology Association (EHA) [33] considered that in immunosuppressed patients the risk/benefit of receiving a SARS-CoV-2 vaccine should be established on a case-by-case basis, taking into account both the incidence of infection in patients and in the community. If vaccination was eventually indicated, the recommendation is to do it at least 2–4 weeks before starting treatment. Finally, in patients receiving highly immunosuppressive treatment, vaccination should be done at least 6 months after the end of therapy to increase the odds of developing immunity.

The European Society for Medical Oncology (ESMO) guidelines¹ recommends prioritizing vaccination of cancer patients regardless of the presence of risk factors. Since efficacy and duration of immunity in cancer patients remains unknown, they suggest their monitoring in specific clinical trials or registries. However, these guidelines did not provide a comprehensive management of vaccination according to the specific hematological disease or treatment procedure, aspects that will be addressed in the current document.

Preliminary data on serological responses in onco-hematological patients with mRNA SARS-CoV-2 vaccines confirmed lower response rates in hematological patients compared to the general population [14,15,19]. However, the reported seroconversion rates (39.5% in CLL patients [17], 75% in general hematological patients [15], 76% in active MM patients [20] and 78% in allo-SCT recipients [16] are really encouraging and seem higher than previously reported data with other vaccines in these immunocompromised patients. These preliminary data support the higher immunogenicity of mRNA vaccines compared to traditional vaccine compounds. Most of these reports were based on mRNA vaccines, and thus formally it remains to be determined if similar response rates can be reached with adenoviral vector-based or other types of SARS-CoV-2 vaccines.

Recommendations for SARS-CoV-2 vaccination by disease

As a common rule for all onco-hematological diseases and procedures, the following general statements were considered:

- Given the high mortality of SARS-CoV-2 infection in these patients, along with the safety of vaccines, all experts advise vaccination even though the degrees of immunization and protection may be lower than that of the general population.
- Onco-hematological patients are among those who should have the highest benefit/risk ratio of vaccination. It is important to clarify this issue to patients and their caregivers and families.
- The benefit of immediate protection against delaying vaccination must be weighed in each case to improve the probability of response.
- Patients can be vaccinated with any of the available vaccines with the exception of LARV.
- The duration of protection could be shorter in immunosuppressed patients than in healthy individuals. Therefore, it is likely that booster doses or revaccination will be required.

- Prospective studies on the safety, efficacy, and immunogenicity of SARS-CoV-2 vaccines are encouraged in this patient population.
- Given the likely lower response rate to vaccination in patients with onco-hematological diseases, it is desirable that caregivers and household partners also receive the vaccine.
- Prior infection with the SARS-CoV-2 virus should not influence the decision of vaccinate.
- Patients who developed COVID-19 and were treated with monoclonal anti-SARS-CoV-2 antibodies or plasma from COVID-19 convalescent donors should wait 90 days before vaccination. Current IVIG formulations, on the other hand, do not contain anti-SARS-CoV-2 IgG, and its use is not predicted to interfere with vaccination.
- Although the vaccine is highly effective, it is recommended to continue the standard protective measures, including mask, physical distance and frequent hand cleaning.

Finally, on August 12, the Food and Drug Administration (FDA) amended the emergency use authorizations (EUA) for both the Pfizer-BioNTech® and the Moderna® COVID-19 vaccines to allow for the use of an additional dose in immunocompromised individuals such as solid organ transplant recipients or equivalently immunosuppressed patients. This EUA has prompted the American Society of Hematology (ASH) to consider a third dose in immunocompromised hematological patients actively treated or receiving either high-dose corticosteroids at vaccination and/or agents causing prolonged B-cell lymphopenia within 12 months before vaccination, those with chronic lymphocytic leukemia, CAR-T cell recipients and hematopoietic stem cell transplant recipients (within two years).

Hematopoietic stem cell transplantation

SARS-COV-2 infection-related mortality in autologous (ASCT) and allogeneic stem cell transplant (allo-SCT) recipients varies from 17% to 30% [4,7,38], with no differences according to the type of transplant. Risk factors for higher mortality include intensive care unit (ICU) admission, advanced age, poor performance status, male gender, and COVID-19 infection during the first year after SCT [4,38]. It is well known from other virus vaccinations (i.e. flu vaccine) in SCT recipients that the best serological response is achieved 6 months after transplant [26,39], which translates in a clinical benefit in terms of lower risk of hospital admission and severity of the disease [40]. A recent observational study that included 88 allo-HSCT recipients

showed an impressive response rate (78%) in terms of seroconversion after mRNA SARS-CoV-2 vaccination [16]. Systemic immunosuppressive treatments within 3 months of vaccination, together with a lymphocyte count below $1 \times 10^9/\text{mL}$ in peripheral blood at the time of vaccination inversely correlated with protective IgG(S-RBD) titers in multivariate analysis. The European Society for Blood and Bone Marrow Transplantation (EBMT) stated that SCT recipients receiving immunosuppressive treatments or with prior pulmonary dysfunction (i.e. bronchiolitis obliterans syndrome) should have a high priority for vaccination [41]. Our recommendations are in line with those of the EBMT:

1. Vaccination of SCT patients should be considered a priority. We recommend SARS-CoV-2 vaccination at 3 months after transplant in ASCT recipients and at 6 months in allo-SCT as long as the incidence of SARS-CoV-2 infection remains high in the community.
2. In case of low community transmission, we recommend delaying vaccination to six months after SCT.
3. Other vaccines are active in patients with moderate-severe active graft-versus-host disease (GVHD) [41]. Therefore, these patients should be included in vaccination programs.
4. Currently there is no data suggesting an activation of alloreactivity. Therefore, the probability that SARS-CoV-2 vaccines can exacerbate GVHD remains very low.
5. Delay SARS-CoV-2 vaccination in:
6. Patients with severe and uncontrolled severe (grade II-IV) acute GVHD.
7. Patients who have received anti-CD20 mAbs in the prior 6 months.
8. Patients who have received anti-thymocyte globulin (ATG) or alemtuzumab in the prior 3 months.
9. In pediatric patients, vaccination should be administered according to the information available in clinical trials and/or the policy adopted in each country for vaccinating children.
10. Patients vaccinated against SARS-CoV-2 before SCT should repeat vaccination after SCT, as with other vaccine-preventable diseases.

CAR-T

There are no solid data on the use of vaccines in general, including against SARS-CoV-2 [42,43]. Our recommendations include:

1. In those candidates for CAR-T therapy in whom bridging chemotherapy will not be administered

Table 1. Summary of recommendations for SARS-CoV-2 vaccination according to the disease.

Disease	Background	Recommendations
Stem-cell transplantation	<ul style="list-style-type: none"> • mRNA vaccines safe in SCT • Priority Immunocompromised patients or with lung involvement • Inactivated vaccines are active and do not worsen cGVHD • Better seroconversion after SARS-CoV-2 mRNA vaccines 	<ul style="list-style-type: none"> • High transmission index: vaccination 3 months after SCT • Medium/low transmission index: delay vaccination 6 months after SCT • Delay vaccination in <ul style="list-style-type: none"> • Severe cGVHD (grades III / IV) • 3–6 months after anti-CD20 therapy • 3 months after ATG or alemtuzumab • Not recommended in < 16 years old • Vaccination prior SCT repeat vaccination after SCT • ASCT: <ul style="list-style-type: none"> • Recommended prior harvesting • If already harvested vaccination 3 months after ASCT
CAR-T recipients	<ul style="list-style-type: none"> • No consistent data on the use of vaccines 	<ul style="list-style-type: none"> • Advisable to monitor response to vaccination in patients under immunosuppressive agents or with lymphocytopenia • Optional prior CAR-T if no bridging chemo in the next 6 weeks • 6 months after CAR-T, earlier if high community transmission rates • If previously vaccinated, re-vaccinate 6 months after CAR-T • Advisable to monitor response to vaccination • Vaccination should not interfere with AML treatment
AML	<ul style="list-style-type: none"> • High mortality of COVID-19 • Prolonged neutropenia hampers antibody production • Complex logistics of vaccination during treatment 	<ul style="list-style-type: none"> • AML in supportive care vaccination recommended according to life expectation • AML in active therapy vaccine should be administered depending on the situation of the patient: <ul style="list-style-type: none"> • Between consolidation cycles • During maintenance when not candidate for SCT • As soon as possible at the end of treatment
ALL	<ul style="list-style-type: none"> • Inferior mortality in children compared to adults • High case fatality rate in adults • In children low immunization against other pathogens during treatment • Blinatumomab B-cell depletion 	<ul style="list-style-type: none"> • Vaccination recommended according to the situation of the patient: <ul style="list-style-type: none"> • At the end of induction • Between consolidation treatments • Anytime during maintenance treatment • Anti-CD20 mAbs delay 3–6 months after the end of treatment, unless there is a high community transmission rate • Blinatumomab vaccination recommended (relapsed patients) • Vaccination not contraindicated with TKIs or inotuzumab • Advisable to monitor response to vaccination in patients treated with monoclonal antibodies
Multiple Myeloma & plasma-cell disorders	<ul style="list-style-type: none"> • COVID-19 increases mortality in MM compared to normal population • Poor response to influenza vaccines • Better seroconversion after SARS-CoV-2 mRNA vaccines 	<ul style="list-style-type: none"> • Not recommended when WBC < 500/ μL • Active disease recommended during MM treatment, between cycles • MM under control hold treatment between 7 days prior and 7 days after immunization • Advisable to monitor response to vaccination in patients treated with IMiDs, monoclonal antibodies or BTK inhibitors
MDS	<ul style="list-style-type: none"> • High mortality rate in MDS with COVID-19 	<ul style="list-style-type: none"> • MDS not receiving treatment with disease modifying agents vaccination as soon as possible • Hypomethylating agents vaccination 1–2 prior next cycle of treatment • Delay vaccination 6 months after last doses of ATG
CLL	<ul style="list-style-type: none"> • High mortality rate in CLL with COVID-19 • Low immunization after seasonal influenza vaccine • Low rate of seroconversion after SARS-CoV-2 vaccine 	<ul style="list-style-type: none"> • Vaccination of CLL at any stage of the disease is a priority • Delay vaccination 3–6 months after the end of anti-CD20 mAbs, unless there is a high community transmission rate • Advisable to monitor response to vaccination in patients treated with monoclonal antibodies or BTK inhibitors
Lymphomas	<ul style="list-style-type: none"> • High mortality rate in patients with lymphoma and COVID-19[72–77] • Low immunization to seasonal influenza vaccine in patients treated with anti-CD20 mAbs • Some differences in response rate after SARS-CoV-2 vaccine among different subtypes of NHL 	<ul style="list-style-type: none"> • Vaccination is recommended irrespective of the disease status • Delay onset of lymphoma treatment (if possible) 3–6 weeks after vaccination. If delay is not possible, administer vaccine at the end of lymphoma treatment • If mAbs against B or T-lymphocytes are employed, delay vaccination 3–6 months, unless there is a high community transmission rate. Patients receiving rituximab maintenance could interrupt treatment and resume it two months after vaccination • Advisable to monitor response to vaccination in patients treated with monoclonal antibodies or BTK inhibitors

(continued)

Table 1. Continued.

Disease	Background	Recommendations
MPN and CML	<ul style="list-style-type: none"> • High mortality in patients with myelofibrosis and COVID-19, compared to ET or PV • Increased risk of thrombosis and COVID-19 in ET and PV 	<ul style="list-style-type: none"> • MPN should be considered a priority group irrespective of disease status or given disease treatment
Mast cell disorders	<ul style="list-style-type: none"> • Outcomes similar to general population • COVID-19 does not impact mast cell activation • Unknown information on safety 	<ul style="list-style-type: none"> • Patients with mast cell disorders can receive vaccines. Contraindications are: <ul style="list-style-type: none"> • Allergic reaction to the first dose (avoid the second dose) • History of allergy to components of the vaccine, particularly PEG or tromethamine • Vaccines should be administered in an environment expert in managing anaphylactic reactions • It is unlikely to observe an adequate immune response 6 months after receiving immunosuppressive treatment for AA (cyclosporine + ATG). After that period, it is possible to observe an immune response, even under cyclosporine maintenance • No contraindications for SARS-CoV-2 in PNH • INR should be in the target therapeutic range • Patients receiving direct anticoagulants or low molecular weight heparin should avoid administration of vaccine during maximum peak plasma concentrations • Platelet counts 25–50,000/μL compression of the puncture site • Platelet counts < 25,000 / μL evaluate platelet transfusion • Hemophilia no contraindication for intramuscular route • All patients vaccine administered using a fine needle < 23G followed by compression for at least 3 minutes • Prior history of heparin-induced thrombocytopenia (HIT): adenoviral-vector vaccines should be avoided, and mRNA-based vaccines used instead
Aplastic Anemia (AA) and PNH	<ul style="list-style-type: none"> • No data available so far 	
Anticoagulants and hemorrhagic diathesis	<ul style="list-style-type: none"> • Vaccines not contraindicated in patients with coagulation disorders • Intramuscular route is adequate in well-controlled anticoagulated patients 	

in the next 6 weeks, vaccination before CAR-T infusion is recommended.

2. Most guidelines recommend the use of vaccines after 6 months of CAR-T therapy [44]. Consider earlier vaccination in case of high community transmission rates.
3. In patients vaccinated against SARS-CoV-2 before CAR-T therapy, revaccinate 6 months after CART infusion as with other preventable diseases.
4. For recipients of CAR-T/TCR cell therapy not targeting B cells, vaccination should be offered as early as the effect of the lymphodepleting regimen has been overcome and/or circulating B cell are in the normal range level.

Acute myeloid leukemia (AML)

In AML SARS-CoV-2 infection have been related with a high mortality rate, ranging from 37% to 50% [45–47]. In a Spanish study with 108 AML patients with COVID-19, the 2-month mortality was 43%. Risk factors for mortality included dyspnea, pneumonia, ICU admission, and D-dimer levels >500 ng/mL [48]. Patients with AML are able to develop antibody response [49]. Considering that prolonged cytopenias hampers

antibody production and the treatment cadence with chemotherapy, recommendations for vaccination are:

1. SARS-CoV-2 vaccination should not interfere with the diagnosis and treatment of AML, including inclusion in clinical trials.
2. AML patients on supportive care should also receive the vaccine.
3. In patients under intensive chemotherapy the vaccine should be administered:
4. Between consolidations cycles in patients in complete remission. In this phase, G-CSF could help to shorten the hematological recovery allowing for an adequate vaccination timing.
5. During the maintenance phase for non-candidates to allogeneic SCT transplantation.
6. As early as possible in patients in complete response (CR) after induction.
7. In AML patients not candidates for intensive chemotherapy, vaccination before starting low/medium intensity treatment may be performed.

Acute lymphoblastic leukemia

SARS-CoV-2 infection has had a special impact on patients with acute lymphoblastic leukemia (ALL). An

Italian study found a particularly low frequency of COVID-19 in patients with Philadelphia chromosome positive ALL and chronic myeloid leukemia, suggesting a protective effect of tyrosine kinase (TKI) inhibitors [50]. In the PETHEMA and GETH study, 52 adults with ALL and COVID-19 had a mortality rate of 33% (EHA meeting 2021). The only identified risk factor for mortality was the presence of comorbidities such as diabetes, cardiac disease, hypertension, and others. Based on the above, recommendations include:

1. Patients receiving conventional chemotherapy: vaccination is desirable once CR is obtained and/or between consolidation cycles. In those receiving maintenance therapy the vaccine should be administered at any time.
2. Patients treated with mAbs
3. Anti-CD20 antibodies: delay vaccination until the achievement of CR or at least 6 months after the last dose of mAbs.
4. Bispecific mAbs: although B-cell depletion is expected to blunt the response to vaccination, patients receiving blinatumomab are particularly vulnerable because they have refractory or relapsed ALL. Therefore, we recommend vaccinating these patients.
5. Immunoconjugated mAbs. There is little evidence on the effect of inotuzumab on normal B lymphocytes. Again, the special vulnerability of patients treated with this drug makes them candidates for vaccination.
6. Patients treated with TKIs. It has been suggested that TKIs confer protection against COVID-19 infection in patients with ALL [50]. Interestingly, all TKIs except dasatinib have little effect on the immune response: Therefore, patients with Ph-positive ALL should follow the same recommendations.
7. Patients in CR without active treatment should be vaccinated as soon as possible.

Multiple myeloma (MM) and plasma cell disorders

Patients with MM and COVID-19 have a higher mortality (33%) than the general population [51,52]. Identified risk factors for mortality included age, genetic high-risk MM, renal disease, and active or progressive MM.

Vaccination studies in MM are limited, and a poor response was observed after influenza vaccination [53]. Active disease requiring therapy, less than partial response (PR), and conventional chemotherapy have been associated with lower likelihood for a serological

response [53]. A recent study with mRNA SARS-CoV-2 vaccines in MM patients showed good serological response rates (76% of patients with active MM patients vs 100% in Smoldering MM patients). Multivariate analysis revealed a negative impact on serological responses of older age, exposure to ≥ 4 novel anti-myeloma drugs and the presence of severe hypogammaglobulinemia, whereas none of the novel agents individually decreased the response rate [20]. Altogether, these data suggest that MM patients should be considered a priority in vaccination programs:

1. Timing of vaccination. Vaccination should be delayed when leukocytes $< 500/\mu\text{L}$.
2. Considerations depending on the MM treatment:
3. In case of active disease, vaccination should be performed without stopping anti-myeloma treatment.
4. If disease is under control (at least PR), hold MM treatment 7 days before the first dose of vaccine and up to 7 days after the second dose.
5. Since lenalidomide could enhance the response to vaccination, it is recommended not to stop lenalidomide maintenance [54].

Myelodysplastic syndromes (MDS)

In a series including 105 patients with MDS and COVID-19 [55], a high percentage of hospitalizations (82.7%) and mortality rate (43.8%) was observed. Therefore, resembling other vaccines, SARS-COV-2 vaccination is highly recommended. Current recommendations are:

1. Patients with MDS not receiving treatment with disease modifying agents (chemotherapy, azacytidine, allo-SCT) should be vaccinated as soon as possible.
2. In patients receiving treatment with hypomethylating agents, vaccination is recommended regardless of the neutrophil count, preferably 1 to 2 weeks prior to the onset of the next cycle of treatment.
3. It is not recommended to vaccinate patients who have received ATG within the prior 6 months, or in patients under chemotherapy during the severe neutropenic phase.

Chronic lymphocytic leukemia (CLL)

CLL patients are more prone to serious infections, particularly of viral etiology, even in early stages of the disease [56]. For this reason, various consensus guidelines

recommend seasonal vaccination for influenza and pneumococcal vaccination [56]. The use of chemoimmunotherapies can cause severe lymphocytopenia, compromising the efficacy of vaccination, especially during the first 6 months after treatment [57]. Poor vaccine responses have also been reported in CLL patients treated with Bruton's tyrosine kinase (BTK) inhibitors [58,59].

Mortality rates of SARS-CoV-2 infection in CLL patients are >30% higher than in the general population [1,60–62]. Age, comorbidities, lymphocytosis and inflammatory parameters (C-reactive protein and D-dimer) were strongly related to mortality [1,60–62].

Seroconversion after the seasonal influenza vaccine in patients receiving ibrutinib has been reported to be as low as 7% in one study evaluating the standard-dose vaccine and 26% in another in which a proportion of patients received a higher dose [58,63]. A recent investigation on humoral immune responses to BNT162b2 mRNA COVID-19 vaccine in patients with CLL showed a low antibody response rate of 39.5%, being even lower in patients under BTK inhibitors or venetoclax ± anti-CD20 antibody [17].

Based on the foregoing and with the data available to date, our recommendations are:

1. CLL patients should be considered a priority population for vaccination, even in earlier stages of the disease, and whenever possible 1–2 months before starting treatment against CLL.
2. In patients receiving anti-CD20 mAbs, delay vaccination 6 months after the end of treatment.
3. After treatments that could limit the efficacy of vaccination for SARS-CoV-2, such as anti-CD20 mAbs, or in patients on continuous treatments with targeted therapies, mainly BTK inhibitors, it would be advisable to monitor the immune response to vaccination.

Lymphomas

Among patients with hematological malignancies reported with COVID-19 lymphomas are the most common type of underlying diseases, [5,64], probably due to the immune dysfunction caused by the lymphoma itself and its treatment [65]. A retrospective study showed an overall mortality of 30% [66]. Age >70 years and the presence of relapsed/refractory lymphoma were associated with higher mortality. Moreover, lymphoma patients undergoing or having received rituximab-containing regimens within the past 6 months did not achieve protective antibody titers after influenza A (H1N1) 2009-virus vaccine

during the 2009 'swine flu' pandemic [67]. Recent published data suggest differences in serological responses after mRNA SARS-CoV-2 vaccination among the different NHL subtypes. Seronegativity was found in patients with mantle cell lymphoma (MCL; 56%), marginal zone lymphoma (MZL; 38%), chronic lymphocytic leukemia (CLL; 36%), Waldenstrom's macroglobulinemia (WM; 26%), follicular lymphoma (FL; 22%), and diffuse large B-cell lymphoma (DLBCL; 21%) [19]. In this setting, recommendations are:

1. Patients with lymphoproliferative neoplasms should receive vaccination irrespective of the presence of active disease or treatment or remission status.
2. Patients in remission of their disease and without active treatment should be vaccinated as soon as possible.
3. If onset of lymphoma treatment can be delayed, as is the case of many indolent lymphomas, the vaccination schedule should be completed within a reasonable time span, taking into account the time required to reach the peak serological response according to each vaccine compound (2–4 weeks after its completion), before the start of immunosuppressive treatment.
4. When lymphoma treatment cannot be delayed (i.e. aggressive lymphomas), vaccination should be administered after completing treatment.
5. When mAbs against B or T-lymphocytes are employed (i.e. anti-CD20, anti-CD19), delay vaccination 6 months after the last dose. Earlier vaccination should be considered in cases of high community transmission rates or in long-term treatments (i.e. maintenance rituximab during ≥ 2 years).

Myeloproliferative neoplasms (MPN)

A retrospective study with 175 patients with MPNs who developed COVID-19 reported a mortality rate of 29%, significantly higher in patients with myelofibrosis than in patients with polycythemia vera or essential thrombocythemia (ET) (40%, 20%, and 25%, respectively) [68]. The increased risk of thrombotic complications observed during SARS-CoV-2 infection is of particular concern in these patients. The cumulative incidence of thrombosis in patients with MPN after developing COVID-19 was 8.5% at 60 days, with the highest risk in ET [69]. The humoral response and the memory B-cell population of CML patients treated with TKIs were significantly lower in those who received the pneumococcal vaccine [70]. Recent data

have shown evidence of robust memory T-cell responses in patients with MPNs after SARS-CoV-2 infection [71].

Recommendations:

- Patients with MPN and CML should be considered a priority group to receive vaccination against SARS-Cov-2 at any stage of the disease and irrespective of the treatment given.

Mast cell disorders

Patients with mast cell disorders have mortality outcomes similar to the general population when infected with SARS-CoV-2 [72]. In addition, it has been recently shown that COVID-19 infection does not trigger mast cell activation symptoms [71]. However, there is still insufficient information on the risk of anaphylaxis to vaccines against SARS-Cov-2 in patients with mastocytosis and/or with mast cell activation syndrome (MCAS).

The recommendations are:

- All patients with mastocytosis and MCAS, except the cases specified in the contraindications section, can receive the vaccine. This includes cases with the diagnosis of aggressive systemic mastocytosis (ASM), mast cell leukemia (MCL) or systemic mastocytosis associated with hematological neoplasia (SM-AHN).
- Contraindications:
 - Patients with an allergic reaction to the first dose of the vaccine should not receive the second dose.
 - History (or high suspicion) of allergy to any of the components of the vaccine, particularly history of allergy to polyethylene glycol (PEG), and the possibility of cross-reactions in patients allergic to polysorbates, cremophor and pegylated drugs.
 - With the Moderna vaccine, a possible history of allergy to tromethamine should also be investigated, especially in patients with a history of allergic reactions to radiological contrasts, dextropropofol, ketorolac, and intravenous fosfomicin.
- Administration: The vaccine must be administered with adequate safety measures. All patients should take a type-1 oral antihistamine before the vaccine, especially drugs without PEG: dexchlorpheniramine 6 mg, loratadine 10 mg, bilastine 20 mg, or rupatadine 10 mg. Patients should remain in observation

at least 45 minutes, which is the interval during which most anaphylactic reactions occur.

Aplastic anemia (AA) and paroxysmal nocturnal hemoglobinuria (PNH)

Few data are available on the effect of COVID-19 in patients with bone marrow aplasia or PNH, nor on their response to conventional vaccines.

1. Patients with AA on immunosuppressive treatment. Given the impaired immune status of patients 6 months after having received cyclosporine associated with ATG [73], it is unlikely that an adequate immune response to vaccination will be attained during this time lapse.
2. There are no contraindications for SARS-CoV-2 vaccination in patients with PNH. It is advisable to monitor hemolysis, particularly in PNH patients who are not receiving complement inhibitors [74].

Patients under anticoagulant agents or with hemorrhagic diathesis

Recommendations for this group of patients are:

1. SARS-Cov-2 vaccines are not contraindicated in patients with coagulation disorders. Currently approved vaccines must be administered via intramuscular route in one or two doses. In patients with thrombocytopenia and bleeding disorders (i.e. hemophilia or anticoagulant treatment), it is recommended to proceed with caution due to the risk of bleeding or bruising.
2. The benefit of vaccination in preventing COVID-19 outweighs the possible risks of the intramuscular administration of these vaccines.
3. In anticoagulated patients, the intramuscular route of drug delivery was established as a safe procedure a long time ago, including influenza vaccination [75].
4. Vitamin K antagonist in therapeutic INR range, low-molecular-weight heparins, or direct-acting anticoagulants should not be discontinued before vaccination. Specifically, patients receiving oral VKA should confirm they are in their INR target therapeutic range before vaccine administration. Patients treated with LMWH or DOACs should schedule their vaccination avoiding the drug's maximum peak plasma concentrations.
5. The recommendation in patients with persistent thrombocytopenia depends on the platelet count:

6. Platelet count > 50,000/ μ L: no special measures are required.
7. Platelet count 25-50,000/ μ L: 3 minutes compression of the puncture site.
8. Platelet count <25,000/ μ L: Careful assessment and prophylactic platelet transfusion should be evaluated.
9. In patients with bleeding disorders (i.e. hemophilia), there is no contraindication for the administration of intramuscular vaccines, which should be done carefully under the supervision of their treatment centers.
10. For all patients with coagulation disorders, the vaccine should be administered through fine needle (maximum needle gauge 23G) followed by area compression for at least 3 minutes. Early bleeding should be monitored right after administration.
11. Vaccine-induced thrombotic thrombocytopenia (VITT) is a rare complication of adenoviral-based COVID-19 vaccines [76]. Although the mechanisms involved have not been fully clarified, it appears that a component of these vaccines (potentially linked to the adenoviral vector) binds to PF4, inducing the production of antibodies (autoantibodies) against PF4 that can activate platelets and generate severe thrombosis.

Given this particular mechanism, patients with previous history of thrombosis or thrombophilia should not be excluded from COVID-19 vaccination, with any of the approved vaccines. Only in patients with a history of heparin-induced thrombocytopenia (HIT) should adenoviral-vector vaccines (i.e. AstraZeneca or Janssen) be avoided, and mRNA-based vaccines be used instead.

Conclusions

The lack current of scientific evidence on the efficacy of SARS-CoV-2 vaccination should not be regarded as exclusion criteria for its administration in onco-hematological patients. These patients are at higher risk of severe COVID-19, and therefore, they should be considered a priority in all vaccination programs worldwide. Disease status and therapeutic plan should be considered to maximize the chances of achieving an immunological response.

Hematological societies should encourage prospective and multicentric studies aimed to determine the effectiveness and the duration of response of SARS-CoV-2 vaccines in each onco-hematological disease

and at different periods of time, according to the specific treatments. Finally, prospective comparative studies with different SARS-CoV-2 vaccines to figure out the most appropriate compound in this specific scenario are warranted.

Disclosure statement

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