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SARS-CoV-2 Vaccines in Patients With Multiple Myeloma

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COVID-19 pandemic has led to an unprecedented need to develop an effective and safe vaccine in a timely manner. SARS-CoV-2 binds to human cells via the spike (S) protein, which targets the cellular angiotensin-converting enzyme (ACE-2) expressed on their surface. The identification of the S protein has led to two categories of vaccines with different mechanisms of action that target this protein. The first one uses inactivated virus that expresses the S protein following genetic manipulation. The second one is based on the administration of molecules that guide the synthesis and the expression of the S protein in human cells. As it seems that the mRNA-based vaccines are becoming the frontrunners in clinical trials to fight the COVID-19 pandemic, challenges regarding their efficacy and safety in oncology populations emerge.

Recently published large clinical trials showed that mRNA vaccines enhance effectively human immunogenicity against SARS-CoV-2, leading to accelerated approval by the regulatory authorities.[1,2] Nucleic acid-based vaccines have been investigated for several years for cancer and infectious diseases, in which a plasmid is introduced via electroporation or injector gun. For mRNA vaccines delivery to the cytoplasm is enough, in contrast to DNA vaccines where nuclear delivery is essential. The subunit vaccines include only elements of the pathogen, therefore, are considered as the safest type of vaccine. One issue remains that they are often poorly immunogenic. Under this prisma, such type of vaccine seems safe for immunocompromised patients, although there are some concerns regarding their efficacy. Another issue that may be considered in cancer patients is that mRNA vaccines are encapsulated into small liposomes. It has been hypothesized that lipid carriers and liposomes may accumulate in tumor tissues through the enhanced and permeation retention effect that poses questions about the adequate dosing for optimal protection.[3] On the contrary, attenuated virus vaccines raise some concerns with immunocompromised, pregnant, or elderly people. In these populations, the virus might become pathogenic, resulting in serious adverse events. A rapidly progressing malignancy and a heavily immunosuppressive therapy may predispose for such events.

Immunocompromised patients such as patients with hematological malignancies or solid cancer are more susceptible to infection and at significantly higher risk of severe complications and worse outcomes compared with general population. Patients with hematological malignancies (leukemia, lymphoma, and myeloma) are more susceptible to SARS-CoV-2 infection with a higher morbidity and mortality compared with patients with solid organ tumors.[4] Among hospitalized patients with COVID-19 and hematological cancer, the risk of death has been estimated up to 39%.

More specifically, patients with multiple myeloma (MM) have an impaired immunity due to both the underlying disease and the immunomodulatory treatments. Normal B-cell expansion is suppressed due to the expanding myeloma clone, whereas immunoglobulin function is suboptimal. In both a pooled analysis of 23 studies encompassing data from 412 patients with MM and a retrospective study conducted by the International Myeloma Working Group that included 650 patients with MM and COVID-19, the estimated risk of death due to COVID-19 was 33%.[5,6] Male gender, older age, active disease status, and renal impairment have been identified as independent prognostic factors for mortality among hospitalized MM patients with COVID-19.[6] Taking into consideration all the above, there is an urgent need to protect patients with MM from SARS-CoV-2 infection. Apart from the general measures including meticulous hand hygiene, mask wearing, and social distancing, vaccines may provide substantial protection against COVID-19, similar to other communicable diseases.[7] However, patients with MM were not included in the pivotal clinical trials evaluating the efficacy and safety of mRNA-based vaccines against SARS-CoV-2, since patients with active malignancy were excluded from both studies.[1,2] From a pathophysiological viewpoint, no new safety concerns and interactions with antimyeloma drugs are anticipated in patients with MM. However, the immunosuppression on the grounds of both myeloma and related treatment may impair sufficient seroconversion and antibody development that poses the efficacy of available vaccines into question. Antimyeloma therapies alter the immune microenvironment and impair both T-cell function and antibody production.[7] B-cell depleting agents including anti-CD38 and anti-SLAMF7 monoclonal antibodies, as well as novel BCMA-targeting agents, may further impede seroconversion and antibody positivity following vaccination. Despite all these challenges, patients with MM produce antibody responses following vaccination against viruses and bacteria, although they may need booster doses to assure adequate protection, such as in the case of the seasonal influenza vaccine.[7] It has to be noted that special considerations regarding

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the timing and the dosing schedule are made in patients undergoing stem cell transplant.[7]

Seroconversion and antibody-mediated response are essential to predict potential vaccine effects especially in immunocompromised patients. Research on seroconversion after COVID-19 in patients with cancer is rather sparse. A prospective study enrolling 61 patients with malignancies and 105 health workers with confirmed or probable COVID-19 based on clinical or radiological findings showed similar rates of IgG positivity (87.9% vs 80.5%, $p = 0.39$) at 17 days after symptom onset or after a positive real-time polymerase chain reaction (RT-PCR) testing.[8] Although the vast majority of cancer patients received active treatments at the time of SARS-CoV-2 infection, only 10% were under chemotherapy. Another study compared seroconversion rates among 40 cancer patients with COVID-19 and 1430 cancer-free patients hospitalized for COVID-19.[9] The 2 groups were matched regarding age and gender. IgG prevalence was 72.5% [95% confidence interval (CI): 58.0%–87.0%] in patients with COVID-19 and cancer, which was significantly lower compared to 90.3% (95% CI: 88.7–91.8%) in patients without cancer ($p < 0.001$). A retrospective study on 85 cancer patients screened for COVID-19 showed that anti-SARS-CoV-2 antibodies were more often undetectable in patients who had received treatment during the month before testing.[10] A retrospective study on 21 patients with chronic lymphocytic leukemia (CLL) diagnosed with COVID-19 showed that 67% of the included patients developed SARS-CoV-2 IgG antibodies at a median of 57 days.[11] Among patients with positive antibody testing, 21% were receiving CLL-specific therapy at the time of diagnosis, as compared with 57% in the patient group without serological response. Hypoglobulinemia defined as IgG < 650 mg/dL was negatively associated with the development of IgG antibodies. This is a finding which may be also relevant for patients with MM that usually present with immunoparesis during the disease course.

It is well recognized that vaccines confer significant protection in patients with cancer. In these terms, patients with hematological and solid malignancies are strongly advised to be vaccinated for both seasonal flu and pneumococcal pneumonia. Therefore, patients with cancer, especially those with comorbidities that are at even higher risk for severe COVID-19 infection, should be definitely vaccinated against SARS-CoV-2. mRNA vaccines seem to have a safer toxicity profile compared with live attenuated vaccines with questionable safety in these patient population, although currently, there are no data available for SARS-CoV-2 specifically.

The American Society of Clinical Oncology is currently suggesting vaccination for COVID-19 for all cancer patients, as long as they do not have any other contradictions to be vaccinated according to the recommendations issued by the Centers for Disease Control (https://www.asco.org/asco-coronavirus-resources/covid-19-patient-care-information/covid-19-vaccine-patients-cancer). Although the Society recognizes that some patients might experience decreased responses to the vaccine, they state that it still might confer some benefit and reduce the relevant risk for infection, especially considering the available data that oncology patients might experience higher rates of severe infection (https://www.asco.org/asco-coronavirus-information). In the United Kingdom, Public Health England and Medicines and Healthcare products Regulatory Agency (MHRA) prioritize vaccination in patients with specific cancers, bone marrow/stem cell transplantation, and immunosuppression due to disease or treatment considering that they are extremely vulnerable due to a higher risk of morbidity and mortality from COVID-19 (https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19). The European Society for Medical Oncologists (ESMO) also poses the vaccination of patients with cancer at a high priority (https://www.esmo.org/covid-19-and-cancer/covid-19-vaccination). For this vulnerable patient population, vaccination of their caregivers and healthcare staff is also of extreme importance, as well as the good hand hygiene, social distancing, and mask wearing.

However, open issues still remain. It is of high importance to evaluate the vaccine candidates for the duration of immunity, as well as for efficacy and safety, especially in patients with MM. Studies on the seroconversion rate and the duration of protective immunity following physical infection with SARS-CoV-2 in patients with MM would be particularly important to elucidate the immune response to this novel pathogen. The exact dose, the number of doses, and the dosing intervals to ensure maximum immunogenicity for patients with MM need to be further investigated.

In conclusion, patients with MM are at a high risk for severe COVID-19 with high mortality rates. Vaccines against SARS-CoV-2 are endorsed in patients with MM without any other contradiction. Ideally, the efficacy and safety of anti-SARS-CoV-2 vaccines should be evaluated in clinical trials including this patient group to determine the optimal timing and dosing schedule.

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