VIRAL INFECTIONS IN HEMATOLOGIC MALIGNANCIES

Infections are a common cause of morbidity and mortality in patients with hematologic malignancies (1, 2). Among pathogens, viruses in particular have a complex and multifaceted impact on the clinical care of these patients. Compared with healthy populations, patients with hematologic cancers exhibit greater susceptibility for acquiring several viral infections, developing infection-associated morbidity and in the case of some viruses such as herpes simplex viruses (HSV), greater risk of viral reactivation (2). Viruses such as Epstein-Barr virus (EBV) and human herpesvirus-8 also play a direct role in the pathogenesis of some lymphomas. Understanding the mechanisms underlying protective immunity against viruses and the determinants of viral clearance as well as reactivation in patients with hematologic malignancies therefore has major implications for improving the care of these patients. The recent emergence of the COVID-19 pandemic caused by the novel coronavirus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has brought several unmet needs relating to understanding pathogen-specific immunity and protection in these patients to the forefront and are the focus of this article.

While hematologic cancers represent a diverse spectrum of tumors with distinct clinical presentation and each tumor type involves specific considerations, the mechanisms underlying the increased susceptibility to viral infections in these patients are likely a result of cumulative immune dysfunction with alterations in both innate and adaptive immunity. The specific defects in immune system may depend both on the nature of the malignancy and its therapy (2). For example, in patients with acute leukemia, a major contributor to immune dysfunction may be linked to cytopenias due to disruption in normal hematopoiesis. Patients with B-cell/plasma cell malignancies in particular have severe deficiencies in humoral immunity due to reduction in normal B/plasma cells, which often manifest as hypogammaglobulinemia, leading to reduced antibody responses to viruses and vaccines. In addition to malignancy-associated immune dysfunction, therapies used to treat these tumors, including cytotoxic chemotherapy, stem cell transplant, steroids, as well as mAbs such as anti-CD20 antibodies have a marked impact on immune responses. Patients with multiple myeloma are commonly treated with plasma cell–depleting therapies, such as proteasome inhibitors and anti-CD38 antibodies. Newer therapies such as CD19-targeted chimeric antigen receptor T cells also lead to marked and prolonged B-cell lymphopenia as “on-target” effect of therapy and thereby impair antiviral immune defenses. In patients treated with allogeneic stem cell transplant, the presence of graft-versus-host disease and need for T-cell immunosuppressive therapy impacts the risk of infections. Disease and therapy-related issues therefore are major determinants of the type and severity of immune dysfunction and subsequently impact the risk of infections.

Recent studies have also demonstrated that several of the alterations in immune cells found in clinical tumors originate early even in precursor states such as monoclonal gammopathy of undetermined significance (MGUS; ref. 3). For example, even in MGUS, bone marrow T cells can exhibit features of immune exhaustion (4). Epidemiologic studies have also suggested that patients with MGUS may have some increase in the risk of infections and reduced immune responses to standard vaccines (3). As the precursor states such as MGUS are much more common than their malignant counterparts, involving over 4% of individuals over 50 years of age in the case of MGUS, immune alterations as a result of hematologic malignancies or their precursors could impact protective immunity against pathogens in a substantial proportion of the human population.

The susceptibility of individual hematologic malignancy patient cohorts to different viruses varies widely but depends, in part, on the nature of the dominant immune deficiency (e.g., T cell vs. B cell), stage, and clinical status of the underlying malignancy as well as duration and intensity of therapy-mediated suppression. Infections caused by varicella-zoster

**Summary:** Patients with hematologic malignancies have increased susceptibility to viral infections and suboptimal immunologic responses to current vaccines due to both disease-associated and therapy-related immune dysfunction. These considerations may impact the efficacy of emerging COVID-19 vaccines in this patient population as well and warrant the need to systematically study natural and vaccine-induced virus-specific immunity in these patients.
Vaccines represent one of the greatest triumphs in modern medicine and have emerged as one of the most cost-effective approaches to save human lives. Vaccines have been most successful in the setting of invariant pathogens that lead to an acute infection and then lasting immunity. In this setting, a live attenuated vaccine (LAV) with reduced pathogenicity leads to strong cellular and humoral responses that last for several decades, even with a single immunization. LAVs against pathogens such as smallpox, polio, yellow fever, measles, mumps, rubella, and chickenpox have been successfully administered worldwide to billions of patients and led to successful eradication of pathogens such as smallpox. LAV such as yellow fever vaccine engages multiple innate immune receptors, which then lead to activation of a diverse array of cellular and antibody responses mediating lifelong protection and represents an example of a gold standard for an effective vaccine (5). The challenges for effective vaccination emerge, however, in the setting of viruses when acute infection does not lead to prevention of reinfections (e.g., RSV), or when the virus can cause a latent infection [e.g., human immunodeficiency virus (HIV), EBV] or can evolve or mutate rapidly (e.g., HIV). In such settings, it becomes imperative to improve on nature to generate effective vaccines. As an alternative, subunit vaccines with adjuvants have been licensed against diverse pathogens, including viruses such as hepatitis B and human papilloma-virus (HPV). Some subunit vaccines, such as against HPV, mediate long-term protection, but subunit vaccines generally lead to less durable immunity compared with LAVs and may require booster vaccines. LAVs do carry a risk of causing disease in immune-compromised hosts and therefore have generally been contraindicated in immune-compromised patients with hematologic malignancies.

The hallmark of an effective vaccine is strong and durable induction of both antibody and cellular responses (5). In contrast to T cells, which only recognize virus-infected cells, antibodies recognize free virus and are therefore essential to prevent infection. Several vaccine studies have measured the levels of antibodies against vaccine antigens as a measure of immunogenicity of vaccines. Levels of antibodies that correlate with seroprotection have been utilized for regulatory approval of vaccines. It is increasingly apparent, however, that levels of antibodies alone are not a reliable surrogate of vaccine efficacy in many settings. Qualitative aspects of antibodies including their affinity, specific target on the virus, ability to neutralize virus including broadly neutralizing activity, as well as ability to engage Fc-mediated effector functions may be equally important determinants of in vivo efficacy (5). Another important aspect of successful vaccination is the ability of the vaccines to lead to durable immune responses, which, in turn, may depend on the properties of vaccine-induced memory B and T cells and long-lived plasma cells. In a recent study, it was shown that bone marrow plasma cells induced by seasonal influenza vaccination already begin to decline by the end of the season, suggesting that loss of these cells may underlie limited durability of immunity to current vaccines (6).

**VACCINATION AGAINST VIRUSES IN HEMATOLOGIC MALIGNANCIES**

The appreciation of increased risk of infections and infection-related mortality in patients with hematologic malignancies has led investigators to explore vaccination as a strategy to prevent viral infections in these patients. A common example of vaccine-preventable illness in these patients is seasonal influenza. As an example, suboptimal immunogenicity of influenza vaccines in myeloma patients has led to studies exploring the use of high-dose vaccines as well as repeat dosing (7). In a randomized study, two injections of high-dose vaccine led to higher overall rates of seroprotection compared with the current standard of single vaccines in patients with plasma cell disorders (8). This strategy also led to more durable immunity with a higher likelihood of seroprotection at the end of study. Further studies in patients with hematologic malignancies to improve vaccine efficacy, including alternate schedules and improved adjuvants and vaccine platforms, are needed.

It is notable that current data about immune responses to vaccines against pathogens in patients with hematologic malignancies are limited mostly to antibody titers. There is therefore an unmet need to better understand the nature and durability of virus-specific B- and T-cell responses in these patients, evaluate the qualitative and quantitative aspects of cellular response to these vaccines, and determine how the vaccine-induced responses differ from those in healthy individuals. Such studies are also essential to better understand the impact of current therapies on vaccine-induced immune responses. It is notable that as hematologic malignancies are characterized by significant alterations in the bone marrow-resident cells, they may also impact the generation and maintenance of long-lived plasma cells in the marrow (6), which are important for durable immunity. The concept that serologic responses to vaccines may be suboptimal has also led investigators to consider passive therapies such as immune globulin (IVIG) as well as early application of antiviral therapy when appropriate.

**THE CHALLENGE OF COVID-19 IN HEMATOLOGIC MALIGNANCIES**

The COVID-19 pandemic caused by SARS-CoV-2 has become a global health crisis. Patients with underlying health conditions and African-American (AA) racial ancestry seem
to be at a higher risk of morbidity and mortality related to the viral infection (9). The clinical course of SARS-CoV-2 infection can be highly heterogenous, with some remaining nearly asymptomatic, while others develop a systemic inflammatory syndrome that leads to COVID-related morbidity and mortality, particularly in older patients and those with comorbidities (9). The immunologic underpinnings of these diverse clinical phenotypes are not fully understood (10). Recent studies have shown that SARS-CoV-2 infection leads to activation of both innate and adaptive immunity, with rapid induction of T- and B-cell responses and neutralizing antibodies (11, 12). In some cases, this vigorous innate and adaptive immune activation and resulting cytokine storm contribute to COVID-related immune pathology. However, the relative contributions of different components of the immune response in controlling the infection are unknown.

Several studies have suggested that patients with cancer are at a higher risk of more severe COVID-19 disease course (13). This is particularly the case for hematologic malignancies such as B-cell malignancies, which are cancers of the immune system itself. Patients with B-cell/plasma cell malignancies are often characterized by deficits in humoral immune response, which is manifested as hypogammaglobulinemia and poor serologic response to vaccines (13). Given the potential importance of antibody responses in control and protection from SARS-CoV-2, it is hypothesized that these patients may be at particularly increased risk from the perspective of impairment in antiviral immunity. Although data from clinical studies are currently limited, available data suggest that these patients may be at an increased risk for SARS-CoV-2–related mortality (14). Together, these emerging data suggest that COVID-19 is likely to have important implications for the care of patients with hematologic malignancies, at least in the short term.

At present, data relating to the kinetics of viral clearance and induction of virus-specific immunity in SARS-CoV-2–infected patients with hematologic malignancies are limited. It is also unknown as to how the virus-specific B- and T-cell responses differ from those in otherwise healthy individuals and whether the immune responses persist in the long term. In the absence of evidence, clinical management of these patients should continue to be based on guidelines adapted from those used to treat other patients, based on the appreciation of underlying immune deficiency and including the guidelines for the use of antiviral therapy, steroids, and passive immunotherapy including convalescent plasma.

**STRATEGIES TO ENHANCE SARS-COV-2 IMMUNITY IN HEMATOLOGIC MALIGNANCIES**

Several vaccines targeting SARS-CoV-2 are currently in advanced phase III testing, and data from these studies are eagerly awaited; however, patients with hematologic malignancies have been excluded from these initial studies. Therefore, the immunogenicity of SARS-CoV-2 vaccines in patients with hematologic malignancies is currently unknown and should be systematically examined in future studies. It is expected that, as with influenza vaccination, the immune efficacy of COVID-19 vaccines will be variable and only a subset of these patients will mount a protective immune response. It would also be important to evaluate the durability of these responses and how the vaccine-induced B- and T-cell responses differ from those in healthy individuals. Until such data are available, patients with hematologic malignancies who have not been exposed to SARS-CoV-2 should continue to be considered susceptible to COVID-19. Patients who do not mount a response to COVID-19 vaccines would be candidates for consideration of other strategies to mediate viral control in the setting of acute infection, including passive immune therapies such as mAbs and antiviral therapies.

It should be noted that, in contrast to seasonal influenza vaccines, which primarily engage a recall response with memory B and T cells, vaccines against COVID-19 will need to activate naïve B and T cells. This is already evident from studies of natural immune response to SARS-CoV-2, which leads to activation of naïve B and T cells and induction of neutralizing antibodies that target the receptor-binding domain (11, 12). Several platforms for SARS-CoV-2 vaccination are now in advanced-phase testing (15). Some of the current leading candidates, such as nucleic acid–based approaches and viral vectors targeting the spike protein, lead to induction of antibodies and CD4 Th cells, but the durability of these responses and capacity for induction of CD8+ memory T cells are not yet known (15). It is notable that many of the naturally occurring T-cell responses against SARS-CoV-2 also target regions other than the spike protein (12). Immune responses to vaccination in patients with hematologic malignancies will likely also depend on the nature and clinical status of the underlying malignancy and therapy-related immune dysfunction, as discussed earlier. Therefore, systematic evaluation of different vaccine platforms and adjuvants as well as vaccination schedules in defined clinical settings would be essential to determine optimal vaccine strategies in these patients.

In summary, it is increasingly apparent that patients with hematologic malignancies have greater susceptibility to viral infections, which leads to an increase in infection-related mortality. Deeper understanding of properties and determinants of protective antiviral immunity in these patients will enable optimal strategies to prevent these infections, including new threats such as COVID-19.

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