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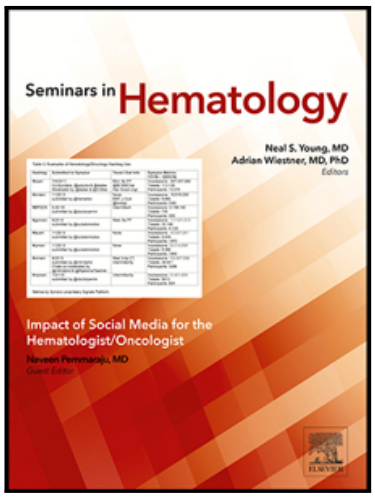

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SARS-CoV-2 vaccine-induced humoral and cellular immunity in patients with hematologic malignancies

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Abstract

Patients with hematologic conditions have a higher risk of severe COVID-19 and COVID-19-related death. This is related to immune deficiencies induced by hematologic conditions and/or the treatment thereof. Prospective vaccine immunogenicity studies have demonstrated that in the majority of patients, a 3-dose COVID-19 vaccination schedule leads to antibody concentrations comparable to levels obtained in healthy adults after a 2-dose schedule. In B cell depleted patients, humoral responses are poor, however vaccination did induce potent cellular immune responses. The effect of 3-dose vaccination schedules and COVID-19 booster vaccinations on the protection of patients with hematologic malignancies against severe COVID-19 and COVID-19 related death remains to be confirmed by population-based vaccine effectiveness studies.

Keywords: COVID-19; SARS-CoV-2; vaccination; immunocompromised; hematologic malignancies; hematology.

Introduction

Within a year after the first case of COVID-19, SARS-CoV-2 vaccines that offered significant protection against severe COVID-19 and COVID-19-related death had become available.[1, 2] Subsequent vaccine effectiveness studies with real-world outcomes of COVID-19 in vaccinated healthy individuals followed shortly thereafter, and confirmed the protective role of the SARS-CoV-2-specific vector vaccines (ChAdOx1 and Ad26.COV2.S) and messenger RNA (mRNA)-vaccines (BNT162b2 and mRNA-1273) against severe COVID-19 and COVID-19-related death.[3-5] Immunocompromised patients, including patients with hematologic malignancies, have an increased risk of severe COVID-19 and COVID-19-related mortality.[6, 7] Because mRNA vaccines, compared to vector vaccines, induced the

highest antibody concentrations in healthy individuals[8, 9], and in the absence of other correlates of protection, (inter)national guidelines recommended a prioritized mRNA vaccination schedule for immunocompromised individuals, including hematology patients.[10] This created the unique opportunity to prospectively investigate the immunogenicity of these vaccines in this patient population, including those patients who are generally considered too immunocompromised to benefit from vaccination, such as patients receiving (immuno-)chemotherapy, shortly after transplantation or after CD19-directed chimeric antigen receptor (CAR) T cell therapy, and in patients receiving novel, targeted therapies. SARS-CoV-2 mRNA vaccines consist of mRNA, encoding the SARS-CoV-2 spike protein, encapsulated in liquid nanoparticles. It is hypothesized that spike-protein produced by muscle cells surrounding the injection site induces a SARS-CoV-2-specific T and B cell response, via antigen-presenting cells in regional lymph nodes. This results in production of spike protein specific immunoglobulin G and A (IgG and IgA) antibodies and the development of T and B cell memory. Antibodies, phagocytic cells, and T, B, and NK cells together induce robust immunity against COVID-19.[11, 12] Hematology patients are thought to be disadvantaged in developing such an immune response after vaccination due to immune deficiencies associated with the hematologic condition itself and/or the treatment thereof. Soon after mRNA vaccination for immunocompromised individuals was implemented, questions emerged about whether these patients are able to mount adequate immune responses, and whether or not extended vaccination schedules could improve initial inferior responses. The aims of this review are to provide insight into humoral and cellular vaccine immunogenicity induced by two or more COVID-19 vaccinations in patients with hematologic malignancies, and to discuss the remaining knowledge gaps relevant for daily clinical practice. We conclude with a summary of current knowledge about vaccine effectiveness and correlates of protection after SARS-CoV-2 vaccination in patients with hematologic conditions.

Immunogenicity of COVID-19 vaccination in patients with hematologic conditions

Humoral responses

The first line of defense against viral infections consists of neutralizing antibody responses. Soon after the introduction of SARS-CoV-2 vaccines in the hematology population, it became apparent that SARS-CoV-2 seroconversion rates, defined as antibody production induced by vaccination, were lower compared to healthy individuals.[13-15] It also became clear that seroconversion after vaccination does not always imply the generation of adequate levels of neutralizing antibodies[14, 16], which is of specific relevance for immunocompromised patients who are known to mount lower antibody titers after vaccination in general.[17, 18] In order to quantify SARS-CoV-2-specific antibody responses in a reproducible and comparable way, the World Health Organization (WHO) advised the use of international reference antibody standards, against which antibody responses to spike 1 (S1), receptor binding domain (RBD), and nucleocapsid (N) antigen domain can be calibrated.[19] Using this international WHO standard, it was demonstrated that, in contrast to the healthy population, humoral immunogenicity to SARS-CoV-2 mRNA vaccines was heterogeneous and reduced in patients with hematologic conditions.[20-22] Because this patient group is diverse, with varying degrees of immunosuppression at humoral and cellular levels, an important question was which patients were most and least likely to respond to (booster) vaccination. We investigated this question in a prospective multi-center study, comprising >700 immunocompromised patients spanning the spectrum of hematologic conditions. For this study, and in the absence of clear correlates of protection, a sufficient antibody response was defined as an S1 IgG antibody concentration of 300 BAU/ml or more. This cut-off corresponded with the lower limit of antibody concentrations sufficient to neutralize the wild-type (Wuhan) variant of SARS-CoV-2 in healthy individuals.[20, 23-25] In a large collaboration with the Dutch National Institute for Public Health and the Environment (RIVM) and several academic hospitals in the Netherlands, this definition was also used by other prospective cohort studies on COVID-19 vaccine immunogenicity in immunocompromised patients.[26, 27] In patients with hematologic malignancies, it was found that after a 2-dose vaccination schedule, more than half of the patients was not able to generate antibody concentrations comparable to levels

obtained by healthy individuals (Figure 1A).[20] Such inferior responses were observed among patients shortly after or with ongoing CD19- or CD20-directed B cell-depleting therapy, CLL patients receiving ibrutinib with or without venetoclax, patients with myeloproliferative disease receiving ruxolitinib, multiple myeloma patients receiving first-line remission-induction therapy, allogeneic HCT recipients early after transplantation, patients with AML receiving hypomethylating therapy, and patients who received two or more immunosuppressive drugs.[20] Other studies also demonstrated a significantly reduced humoral response, compared to treatment-naïve patients, after a 2-dose schedule with the BNT162b2 vaccine in patients with hematologic malignancies treated with immunosuppressive medication such as ruxolitinib, ibrutinib, venetoclax or anti-CD20 therapy.[13, 21, 22, 28-30] On the other hand, many patients mounted higher vaccine-induced antibody concentrations than anticipated. These included patients with multiple myeloma on immunomodulatory drugs (IMiDs), or who had recently received high dose melphalan followed by autologous HCT, but also patients with AML shortly after high dose chemotherapy, patients with chronic graft-versus-host-disease (GvHD), and treatment-naïve CLL patients (Figure 1A).[20, 28, 31] Also in a study from Israel, treatment-naïve CLL patients showed adequate antibody responses in more than half of the patients.[14] Among patients with multiple myeloma, low antibody concentrations were observed when patients were not in complete remission or when anti-CD38 therapy or B cell maturation antigen (BCMA)-targeted therapy was received,[22] whereas treatment with lenalidomide was associated with better antibody responses.[20] Importantly, the presence of low B cell numbers did not necessarily preclude the generation of sufficient antibody concentrations. This means that vaccination should not be delayed or postponed when B cell numbers are low.[20] In many patients, a significant rise in antibody concentration was observed after the first two vaccinations. This raised the question whether an additional (third) vaccination could further enhance antibody concentrations to levels observed in healthy individuals. Indeed, a third mRNA-1273 vaccination led, in the majority of patients with hematologic malignancies, to S1 IgG concentrations comparable to levels obtained by healthy individuals after the primary 2-dose scheme

(Figure 1B).[32, 33] The steepest increase of S1 IgG antibody concentrations was observed in patients with a recovering immune system, such as patients with a reconstituting B cell population after completing B cell depleting therapy and allogeneic HCT recipients. Increased antibody concentrations were also detected in patients with persistent immunodeficiencies, such as AML patients on hypomethylating therapy, treatment-naive CLL patients, and multiple myeloma patients receiving anti-CD38 therapy.[32] Similar observations were reported by others,[34, 35] also confirming the notion that the immunogenicity of a third dose depends on disease- and therapy related factors. Importantly, in the majority of patients, a third vaccination led to a significant improvement of the neutralizing capacity per antibody, even against the Omicron BA.1 lineage, which suggests enhanced antibody maturation and cross-recognition after additional vaccinations.[32, 34]

Together, these data demonstrate the added value of an expanded vaccination schedule in patients with hematologic malignancies. This is also observed with other vaccines such as pneumococcal vaccination for example.[36] The optimal schedule and timing of the third COVID-19 vaccination dose remains to be determined.

In healthy individuals, a booster vaccination is needed to revive waning humoral immunity after the primary vaccination schedule.[37] In immunocompromised patients, a first booster (fourth vaccination) will be equally necessary and may be as effective, as recently confirmed in kidney transplant recipients and patients with hematologic malignancies.[38, 39] It remains to be determined whether a booster schedule similar to healthy individuals suffices or whether adjusted booster schedules are needed for the severely immunocompromised.

Cellular response

For optimal and durable immunity, cellular immune responses are indispensable. In healthy individuals, vaccination-induced T cell immunity supports the generation and maintenance of high-affinity antibodies and correlates with effective viral clearance and mild disease.[40] In contrast to humoral immunity, T cell responses are preserved across SARS-CoV-2 variants, suggesting that viral

evolution does not lead to viral escape from T cell immunity at the population level,[41, 42] and T cell memory is suggested to be stable at least until six months after vaccination.[43]

In patients with a hematologic malignancy, T cell responses to vaccination may differ depending on the underlying condition and treatment thereof. To identify SARS-CoV-2-specific vaccine-induced cellular responses in these patients, interferon-γ releasing ELISpot assays, whole blood interferon-γ release immunoassays [15, 29, 44, 45] and flow cytometry-based analysis of SARS-CoV-2-specific CD4+ and CD8+ T cell responses have been used. Following a 2-dose mRNA vaccination schedule, robust cellular responses are observed in the majority of patients with hematologic malignancies, including patients with CLL, lymphomas, and recipients of CD19-directed CAR T cell therapy (Figure 1C).[29, 45-48] It is suggested that these responses depend on vaccine type, with better responses induced by mRNA-1273 vaccination compared to BNT162b2 [43, 48, 49]. Cellular responses also differ between patient groups. Patients with multiple myeloma were reported to have inferior CD4+ T cell responses to a 2-dose vaccination schedule, possibly related to the use of dexamethasone and/or anti-CD38-directed therapy (Figure 1C).[50] The negative association of steroids with T cell responses after vaccination was reported by others as well.[28] A 3rd vaccination in patients with multiple myeloma on therapy led to an increase in cytokine-producing CD4 T cells,[34] which suggests that a 3-dose vaccination schedule enhances T cell immunity in these patients, as observed in healthy individuals.[37]

Cellular immune responses seem to be even more pronounced in the absence of humoral immunity. More than 70% of B cell-depleted patients did generate cellular responses after SARS-CoV-2 vaccination,[45] a discordance confirmed later by others (Figure 1D).[47, 50, 51] In the absence of a humoral response, the proportions of spike-specific CD8+ T cells were significantly higher compared to proportions observed in individuals with an intact humoral response, suggesting an immune compensatory mechanism.[50] Whether vaccine-induced CD8+ T cell responses provide protection against severe infection and related mortality in these B cell-depleted patients is unclear.

Observations in patients with inborn errors of immunity, such as patients with agammaglobulinemia

or common variable immunodeficiency, who have a dysfunctional or absent humoral immune response, suggest that other components of the immune system, including T cell immunity, are important in the prevention of severe COVID-19 and COVID-19-related death.[52-56] In SARS-CoV-2 infected patients with a hematological malignancy, including B cell depleted patients, a higher number of circulating CD8+ T cells was associated with improved survival.[57] Nevertheless, the observation that B cell-depleted patients remain at higher risk of COVID-19-related mortality compared to healthy individuals despite vaccination indicates that antibody responses are indispensable, even in the presence of T cell immunity.[58, 59] Larger, prospective population studies are necessary to better understand the contribution of vaccine-induced cellular immunity in the protection against severe COVID-19. Such studies are hampered by their elaborate and time-consuming design, and by the lack of universally available standards to quantify vaccination-induced T cell responses.[42, 60]

Indications for revaccination

In the course of the COVID-19 pandemic, new challenges have arisen. For example, patients who were diagnosed with a hematologic malignancy during or after initial vaccination rounds may need to be revaccinated, in particular when they received B cell-depleting therapy or autologous or allogeneic HCT. Not much is known about the effect of such therapies on previously obtained vaccine-induced immunity. Preliminary data from us and others demonstrated that in patients who received cell therapy during the primary 3-dose vaccination schedule, SARS-CoV-2 antibody concentrations were variable and depended on the type of cell therapy and on the timing of cell therapy in relation to the primary vaccination schedule.[32, 61] Furthermore, the immunogenicity of SARS-CoV-2 revaccination is likely to depend on residual and transplanted (donor) immunity. For example, patients with multiple myeloma who received the primary 2-dose mRNA vaccination schedule during induction immune-chemotherapy maintained antibody concentrations after consolidation therapy with high-dose melphalan and autologous HCT. A third mRNA-1273

vaccination further increased antibody concentrations in these patients to levels comparable with those obtained by healthy individuals after a 2-dose schedule, even when antibody responses after the first two vaccinations were poor.[32] By contrast, in patients who received two mRNA-1273 vaccinations prior to allogeneic HCT, a third vaccination within 3 months after allogeneic HCT did not induce an increase in antibody concentrations, most likely because of incomplete immune reconstitution and the use of immunosuppressive agents.[32, 62] In allogeneic HCT recipients, the immune status of the donor significantly impacts vaccination responses, as demonstrated in a recent study in which allogeneic HCT recipients who received hematopoietic cells from a SARS-CoV-2-vaccinated individual reached higher antibody concentrations after vaccination compared to patients who received a transplant from an unvaccinated donor.[63]

Finally, also in patients with B-NHL who received B cell depleting therapy during or after the primary 2- or 3-dose vaccination schedule, the optimal revaccination schedule remains to be determined. At least eight months are needed for B cell reconstitution to levels that are sufficient to generate antibody responses [20, 45, 50]. T cell responses are generated in the absence of B cells, as discussed above (Figure 1C, 1D).[50, 57] It can be hypothesized that in the presence of a primed T cell compartment, revaccination with 1 or 2 vaccinations may suffice, but this needs to be investigated. Importantly, vaccine effectiveness studies are needed to establish the level of protection against (severe) disease in (re)vaccinated transplanted and B cell-depleted patients.

Correlates of protection and vaccine effectiveness

Vaccine effectiveness studies in healthy individuals have clearly demonstrated a significant reduction of severe COVID-19 and COVID-19-related death after SARS-CoV-2 vaccination[64, 65]. Vaccine effectiveness studies among patients with hematologic malignancies demonstrated that after two vaccine doses, the risk of SARS-CoV-2 infection was comparable between patients treated for lymphoma and multiple myeloma. Patients with lymphoma were however more likely to develop severe COVID-19, with increased rates of hospitalization and COVID-19-related death.[58, 59] In

another study it was demonstrated that immunocompromised patients, including patients with hematologic malignancies, had a lower risk of hospitalization due to COVID-19 when they had received three vaccinations compared to those who had received two vaccinations. The risk was however still higher than among 3-dose vaccinated healthy individuals.[66] Another study demonstrated an increased risk of severe COVID-19 and COVID-19-related death in patients with hematologic malignancies compared to patients with solid tumors.[67]

While vaccine effectiveness studies as described above are very informative, they lack the detail needed when counseling individual patients. For this, laboratory-based, reproducible and universally applicable correlates of protection against (severe) COVID-19 need to be defined. However, the minimum antibody concentration needed for protection against severe COVID-19 and COVID-19-related death is not known and will be difficult to establish given the high mutation rate of the virus. Moreover, while antibody concentrations gradually decay, the avidity and functionality of these antibodies improve,[44] implying that over time, lower antibody concentrations may suffice to neutralize infection. In the absence of correlates of protection, random antibody measurements do not yield meaningful information at this time. More detailed studies on vaccine immunogenicity and clinical efficacy among patients with hematologic conditions are needed, in order to better predict vaccination-induced protection against severe COVID-19 at an individual level.

Conclusion

Humoral and cellular immunity obtained by patients with hematologic malignancies after COVID-19 vaccination are highly variable and depend on underlying malignancy and (history of) therapy. For patients with hematologic malignancies, the standard two-dose SARS-CoV-2 mRNA vaccination schedule should be supplemented with a 3rd mRNA vaccination, to further enhance humoral and cellular immunity to levels comparable to those obtained by healthy individuals after a 2-dose schedule. Whether this enhanced humoral immunity provides better protection against severe COVID-19 and COVID-19-related mortality needs to be confirmed. Better understanding of the

protective role of cellular immunity is of paramount importance, as well as vaccine effectiveness studies to correlate humoral and cellular immunogenicity markers to real-world protection in this vulnerable population.

Take home message/ practical learning points

- ✓ Hematology patients are immunocompromised due to their disease and treatment thereof, and demonstrated reduced humoral and cellular immune responses after vaccination;
- ✓ Reduced humoral immunity can be overcome in a large proportion of patients by supplementing the standard 2-dose SARS-CoV-2 mRNA vaccination schedule with a 3rd mRNA vaccination;
- ✓ Vaccination should not be delayed or postponed when B cells are low or absent;
- ✓ In the absence of humoral immunity, cellular immunity is generated;
- ✓ Patients should be revaccinated after autologous HCT, allogeneic HCT and B cell-depleting therapy. Exact timing of vaccination and the required number of vaccinations need to be determined;
- ✓ A single arbitrary measurement of SARS-CoV-2-specific antibodies will not answer the question whether or not protection against COVID-19-related severe disease, hospitalization or death has been obtained;
- ✓ Combined vaccine effectiveness and vaccine immunogenicity studies are needed to provide correlates of protection that are applicable in clinical practice.

Abbreviations: BAU: binding antibody units; COVID-19: corona virus disease 2019; IC50: half-maximal inhibitory concentration; SARS-CoV-2: severe acute respiratory syndrome corona virus 2.

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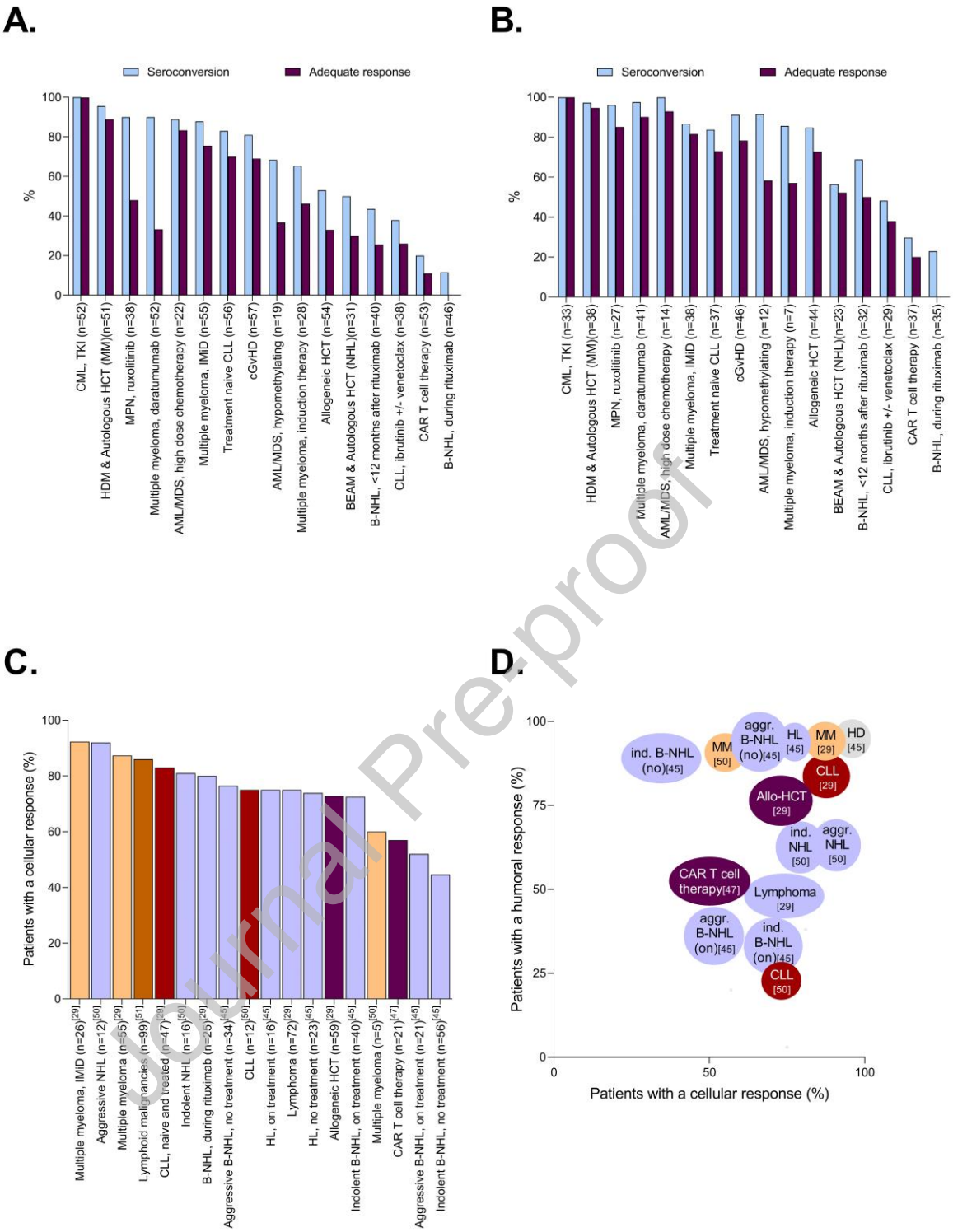
Figure legends

Figure 1. Large variation in SARS-CoV-2 mRNA vaccine-induced humoral and cellular responses in patients with hematologic malignancies. **A.** Humoral immune response 28 days after second mRNA-1273 vaccination in SARS-CoV-2-unexposed patients with hematologic malignancies (n = 692) stratified by patient cohort. Blue bars: percentage of patients that reached seroconversion (≥10 BAU/ml); purple bars: percentage of patients that reached an antibody concentration of ≥300 BAU/ml. N indicates the total number of included patients in each cohort of patients.[20] **B.** Humoral immune response 28 days after third mRNA-1273 vaccination in SARS-CoV-2-uninfected patients with hematologic malignancies (n = 493) stratified by patient cohort. Blue bars: percentage of patients that reached seroconversion (≥10 BAU/ml); purple bars: percentage of patients that reached an antibody concentration of ≥300 BAU/ml. N indicates the total number of included patients in each cohort of patients.[32] **C.** Cellular immune response after second SARS-CoV-2 vaccination in patients with hematologic malignancies, stratified by patient cohort.[29, 45, 47, 50, 51] Bars indicate the percentage of patients that obtained a cellular immune response, defined by ≥40 spot forming units per 10^6 PBMC measured by IFN-γ ELISPOT assay ≥14 days after second mRNA vaccination, [47, 68] or 14-28 days after second ChAdOx1 or BNT162b2 vaccination, [45] or defined by the presence of SARS-CoV-2-specific IFN-γ production in the LIAISON QuantiFERON-TB Gold Plus whole blood assay ≥21 days after second mRNA-1273 vaccination, [29] or defined by the presence of ≥0.05% spike-protein reactive CD4+ T cells or ≥0.005% spike-protein reactive CD8+ T cells after stimulation with a SARS-CoV-2-spike peptide pool, ≥14 days after mRNA vaccination.[50] Orange: multiple myeloma; dark

orange: lymphoid malignancies; light purple: lymphomas; dark purple: cell therapy; red: CLL. Superscript: references; n: number of patients. **D.** Distribution of patients with hematologic malignancies based on SARS-CoV-2-specific humoral and cellular immune response after vaccination, for those cohorts of whom cellular and humoral immunity were measured in parallel. References are indicated between brackets. [29, 45, 47, 50] (No): patients not receiving immunochemotherapy; (on): patients on immunochemotherapy. When "(no)" or "(on)" is not mentioned in the Figure, literature did not determine humoral and cellular responses together in subgroups of treated or untreated patients within the hematologic malignancy.

Aggr: aggressive; Allo: allogeneic; AML: acute myeloid leukemia; BAU: binding antibody units; BEAM: carmustine, etoposide, cytarabine and melphalan; B-NHL: B cell non-Hodgkin lymphoma; CLL: chronic lymphocytic leukemia; CML: chronic myeloid leukemia; cGvHD: chronic graft versus host disease; HCT: hematopoietic progenitor cell transplantation; HD: healthy donors; HDM: high dose melphalan; HL: Hodgkin Lymphoma; IMiDs: immunomodulatory drugs; Ind: indolent; MDS: myelodysplastic syndrome; MM: multiple myeloma; TKI: tyrosine kinase inhibitor.



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