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COVID-19 in patients with hematological malignancies

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Abstract

In most cases, COVID-19 is characterized by a mild clinical course. However, there are groups of patients at high risk of mortality and morbidity of COVID-19, including groups comprising older age (> 65 years), diabetes, hypertension, obesity, cancer, and hematological malignancies. Hematological patients are at high risk due to disease-related immune disorders and treatment-related factors. This review aims to summarize studies on COVID-19 in patients with the most common hematological neoplasms. We describe the fatality rate of COVID-19, the risk of severe disease, the efficacy and side effects of vaccines against COVID-19, and vaccine-drug interactions in chronic lymphocytic leukemia (CLL), multiple myeloma (MM), acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), diffuse large B cell lymphoma (DLBCL) as well as chronic myeloid leukemia (CML). We focus mainly on the use of mRNA vaccines, not other types of vaccines. Hematological patients are a priority group for vaccination against COVID-19, but serological response varies according to the type of hematological malignancy, with better responses in myeloid malignancies and poorer responses in CLL and lymphoma patients. Extended studies are needed to answer questions about a limited response to vaccines and the use of booster doses in CLL and patients treated with anti-CD38 therapy, BTKi therapy, anti-CD20 antibody or ruxolitinib therapy, as well as patients with non-Hodgkin lymphoma (NHL).

Keywords: hematological neoplasms, chronic lymphocytic leukemia (CLL), multiple myeloma (MM), Ph-chronic myeloproliferative disorders (CMD), chronic myeloid leukemia (CML), COVID-19 vaccines

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) expeditiously expanded from an epidemic outbreak in Wuhan, in the Hubei province of China in 2019, into a pandemic infecting more than 770 million individuals all over the world. SARS-CoV-2 invades host human cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor [1–3]. Specifically, SARS-CoV2 is firstly recognized by the toll-like receptors (TLRs) on host cells, which activates nuclear factor kappa B cells (NF-κB), which then activates the angiotensin-converting enzyme 2 (ACE2) receptors. After the activation of ACE2 receptors, the virus can enter cells and begin replication [4, 5]. Moreover, this process of entry initiates the so-called 'cytokine storm'. SARS-CoV-2 can trigger an immune response via pathogen-associated molecular patterns (PAMPs). The virus also causes the release of pro-inflammatory damage-associated molecular patterns (DAMPs) [4]. DAMPs cause the migration of immune cells which increases the release of pro-inflammatory cytokines such as interleukin 2 (IL-2), interleukin 7 (IL-7), interleukin 10 (IL-10), granulocyte colony-stimulating factor (G-CSF), and tumor necrosis factor (TNF) [5, 6] (Figure 1).

It is well documented that COVID-19 primarily manifests as a respiratory tract infection. However, emerging data indicates that it should be regarded as a systemic disease involving multiple systems, including the cardiovascular, respiratory, gastrointestinal, neurological, hematopoietic, and immune systems [1, 2, 7–9]. Patients can manifest

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with asymptomatic virus shedding or syndromes of varying severity [10, 11]. Symptoms can depend on the variant of the virus, but the most common are fever, cough, impairment of smell or taste, and dyspnea. It can also progress to persistent fever, respiratory failure, and even multi-organ failure [11].

Interestingly, there are risk groups that are more likely to come down with severe COVID-19. It has been shown that the older age group (> 65 years) is at high risk of severe SARS-CoV-2 infection, because of comorbidities e.g. diabetes, hypertension, obesity and cancer [12]. Furthermore, males are more critically ill compared to females [13]. The other group at high risk includes patients with cancer as well as hematological malignancies [14].

Since the number of scientific publications about COVID-19 in patients with hematological malignancy is growing rapidly, the aim of this current paper was to examine the latest studies about the clinical characteristics of COVID-19 in patients with hematological neoplasms. We summarize the numerous findings, including data about fatality rate, the risk of acute disease, the efficacy of vaccines against COVID-19, and vaccine-drug interactions specifically in cohorts of patients with chronic lymphocytic leukemia (CLL), multiple myeloma (MM), acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), diffuse large B-cell lymphoma (DLBCL), as well as chronic myeloid leukemia (CML). Additionally, we share the results of clinical trials regarding the efficacy of vaccinations, drawing attention to the fact that the response varies depending on the specific disease (Table I).

Hematological malignancies as a high-risk group in COVID-19

Patients with hematological neoplasms, as immune-compromised people, are at high risk of severe COVID-19 [14]. This is due to immunosuppression, older age, and other comorbidities. Moreover, the specificity of the biology of hematological malignancy, dysfunctions of the immune system, and the type of therapy administered are all key factors that are conducive to the more frequent occurrence of COVID-19, or the development of severe COVID-19 [15]. Immune defects are diverse and include low number of functional B lymphocytes and antibody production, decreased percentage of CD4 lymphocytes, NK cells, impaired antigen presentation by a decrease in the number of dendritic cells, and an increase in the number of regulatory cells. Immune dysregulations depend on the type of disease [16]. Moreover, the treatment given to hematological patients, such as anti-CD20 antibodies, stem cell transplantation, and chimeric antigen receptor (CAR) T-cell therapies, very often impairs immunity [17, 18].

These factors have resulted in patients with hematological malignancies being particularly vulnerable to COVID-19 [18]. In these patients, mortality and morbidity are increased compared to healthy patients [19, 20].

The occurrence of severe COVID-19 in patients with hematological malignancies was observed in a large cohort of 3,801 patients with lymphoproliferative and myeloproliferative malignancies. Pagano et al. [20] showed severe COVID-19 in 63.8% (2,425/3,801) of the patients. Moreover, 73.1% (2,778/3,801) were hospitalized while 31.2% (1,185/3,801) died, of whom 58.1% (688/1,185) died due to COVID-19 infection, 14.6% (173/1,185) due to the hematological malignancy itself, and 13.1% (155/1,185) due to a combination of both. Increased COVID-19 mortality in hematological patients has also been proved. Yigenoglu et al. [17] observed a doubled mortality rate in 740 hematological patients compared to healthy controls (13.8% vs. 6.8%).

Interestingly, the highest mortality rate (58.9%) has been observed among patients receiving demethylating agents. In patients receiving CAR-T therapy, the mortality rate was also high at 47.6%. Patients undergoing autologous hematopoietic stem-cell (auto-HSCT) or allogenic hematopoietic stem-cell (allo-HSCT) transplantation had mortality rates of 27% and 24.8% respectively [20].

The development of COVID-19 vaccines decreased the risk of severe COVID-19. Therefore, vaccinations are recommended for this group of patients despite the fact that the vaccine response in these patients is weaker than in the healthy population [21, 22]. It has been proved that patients who receive two or more doses of COVID-19 vaccine have a reduced risk of COVID-19 [22–26]. Two weeks after the second dose of the BNT162b2 vaccine, 95% of the patients with solid tumors and 60% of those with hematological malignancies responded positively [27, 28]. The safety of mRNA vaccines in hematological patients has been shown to be comparable to that in healthy patients [19]. The most common adverse event was pain at the injection site, followed by fever and muscle soreness. Patients with hematological malignancies had lower median anti-S1 IgG antibody responses after two BNT162b2 vaccine doses than did healthy persons (median 6,961 (units) U/mL vs. 21,395 U/mL). Patients actively treated with BTKIs (0 U/mL) venetoclax (4 U/mL), or anti-CD20 antibody therapy (17 U/mL) showed poor antibody responses. New approaches to treating high-risk patients who are poor responders to vaccination are urgently required. However, patients receiving tyrosine kinase inhibitors (10,537 U/mL) or auto-HSCT (6,203 U/mL) or allo-HSCT (6,304 U/mL) did not differ from untreated patients with hematological malignancies [29]. Moreover, the breakthrough infection in this group of patients is increased, ranging from 11.0% for ALL to 17.2% for MM, with the risk being 4.5% in patients without neoplasms [30].

COVID-19 in chronic lymphocytic leukemia

It has been proved that patients with chronic lymphocytic leukemia (CLL) are at high risk of bacterial infections as well as severe COVID-19, partly due to their older age (median 69 years) and partly due to anti-leukemic treatment [31], [32]. Chatzikonstantinou et al. [31] analyzed a cohort of CLL patients, including almost 42% who had never received anti-CLL therapy, with the rest having been treated with at least one type of therapy. Most (c.56%) of the treated patients were administered with Bruton's tyrosine kinase (BTK) inhibitors (BTKi). Interestingly, almost 75% of CLL patients were admitted to hospital due to COVID-19 infection, and it was shown that 66.2% of patients had severe COVID-19. Nonetheless, the fatality rate among patients with severe COVID-19 was 38.4%. Additionally, patients without any treatment had a lower risk of death compared to those on therapy (33.6% vs. 52.3%). However, the researchers suggested that patients treated with the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib were less likely to be hospitalized. Moreover, they suggested that in patients with CLL and COVID-19, older age was related to a worse prognosis, with increased mortality. Untreated patients had a better chance of survival than did those on treatment or who had been recently treated.

Similarly, Mato et al. [33] confirmed that CLL patients are at high risk of COVID-19. They examined 198 CLL patients, of whom 45% (90/198) were on CLL therapy. The most common therapy was BTKi in monotherapy (60%, 54/90 patients) or in combination (21%, 19/90). The overall mortality rate was 33%. Interestingly, BTKi therapy was not a significant mortality factor.

Research by Roeker et al. [34] compared two cohorts of CLL patients to examine trends over time. They analyzed 374 patients (68%, 254/374 in the first group diagnosed from 17 February through 30 April 2020 and 32%, 120/374 diagnosed from 1 May 2020 through 1 February 2021 in the second group). Hospital admission was required for 75% of CLL patients and the mortality rate was 28%. Interestingly, a larger proportion of patients in the first group required Intensive Care Unit (ICU) admission (32% vs. 15%). It has been proved that BTKi therapy is irrelevant as a survival factor. Roeker et al. also proved that CLL patients are at high risk of severe COVID-19 and should be considered for administration of COVID-19 vaccines.

Many recent studies have evaluated the effectiveness of COVID-19 vaccinations, which are recommended for CLL patients as immunocompetent individuals who are in a high-risk group for severe disease. Furthermore, according to the recommendations of the Polish Society of Hematology and Transfusion Medicine, and the Polish Adult Leukemia Group-CLL, individuals diagnosed with CLL should receive vaccination promptly because they face a higher risk of hospitalization or mortality from severe COVID-19 compared to the general population [32]. Haydu et al. [35] analyzed humoral and cellular immunogenicity of SARS-CoV-2 vaccines in a group of 36 patients with CLL, including 83% (30/36) of patients not on therapy and 17% (6/36) on BTKi treatment. The majority of patients received mRNA vaccines (BNT162b2 or mRNA-1273) while the rest received an adenovirus-based vaccine (Ad26.COV2.S). The overall response after vaccination was 60% in those not on therapy, and 33% in those on BTKi therapy. In addition, in the untreated cohort, a 77% serological response after the mRNA vaccine was achieved compared to a 33% serological response after the adenovirus vaccine. 37% (11/30) of patients who had a negative response after the first dose of the vaccine received a second dose, and 55% (6/11) of them had a detectable response. In addition, it was proved that all patients had antibodies against wild-type SARS-CoV-2 and variants (alpha, beta, gamma, delta). Moreover, Haydu et al. suggested that novel vaccine strategies, including additional vaccine doses, may increase protection against SARS-CoV-2 infection.

Jimenez et al. [36] studied humoral and cellular immunogenicity one month after the second dose of the mRNA--1273 vaccine in CLL and MM patients. 76.3% of patients developed humoral immunity, and the cellular response rate was 79%. These results suggest that a significant difference between the humoral and cellular responses was observed in patients treated with anti-CD20 therapy (humoral response 17.5% vs. cellular response 71.1%). B-cell aplasia was present in these patients, while T-cell counts were maintained.

Experiments performed by Herishanu et al. [37] proved that the antibody response rate was 39.5% in 167 CLL patients after two doses of BNT162b2 mRNA vaccine. Furthermore, they observed that serological response in patients without treatment was significantly higher (58.7%) including patients off-therapy in remission (79.2%) compared to a group on therapy (16%). In general, 13% (21/167) of patients after the first dose, and 23% (39/167) of patients after the second dose, reported mild adverse effects e.g. weakness, headache and/or fever. In addition, there was no difference between patients on therapy compared to those off-therapy. Additionally, they carried out another study which observed patients with CLL after the administration of a third dose of BNT162b2 mRNA vaccine [38]. This proved that in 172 patients who failed to respond to the second dose of the vaccine, the antibody response rate was 23.8% after the third dose. As in the previous study, treatment status played a role in the serological response. Patients off-therapy had significantly higher (40.3%) response rates compared to those on therapy (12%). Interestingly, the response rate in patients receiving BTK inhibitors was 15.3% compared to 7.7% in patients treated with anti-CD20 antibodies. The most common adverse effect was pain at the injection site (54%).

Nonetheless, a different research study focused on 61 chronic lymphocytic leukemia (CLL) patients assessing their antibody response six months after receiving the second dose of the BNT162b2 mRNA vaccine [39]. Here, antibodies were still detectable in 90% (55/61) of patients. However, after six months, the antibody level had decreased significantly from 107.1 U/mL to 67.5 U/mL. It was shown that anti-CLL treatment played a role in serological response. 83% (5/6) of patients who were sero-negative were on therapy (BTKi or venetoclax plus obinutuzumab).

In another study, 500 CLL patients were examined after two doses of COVID-19 vaccine [40]. Antibody response was 67%; 41% received the BNT162b2 mRNA vaccine and 59% the ChAdOx1 (Oxford/AstraZeneca) vaccine. The use of different vaccine platforms did not influence antibody response. In addition, patients on BTKi therapy had a significantly lower response rate (33%). In addition, it has been proved that male gender (44% lower), BTKi therapy (80% lower), and the presence of IgA or IgM hypogammaglobulinemia (72% and 57% lower respectively) were factors that determined a lower immune response. Furthermore, neutralization of the delta variant was significantly lower (14%) compared to the Wuhan virus (62%).

Similar outcomes were presented by Bagacean at al. [41, 42]. 530 patients received mRNA vaccine (BNT162b2 or mRNA-1273). The response rate was 27% after the first dose and 52% after the second dose. The research proved that patients on therapy had a significantly lower immune response (22%) compared to treatment-naive persons (72%). All patients receiving venetoclax plus anti-CD20 mAbs and venetoclax plus BTKis did not respond after the second dose of the vaccine. Patients who did not seroconvert (18%, 95/530) after two doses of vaccine, received a third dose. In these patients, the response rate was 35%.

Furthermore, the reaction to mRNA vaccines against SARS-CoV-2 was examined in individuals with MM and CLL [43]. The authors assessed the humoral and T cell-mediated immunity following two doses of BNT162b2 or mRNA-1273 in short-term (2-5 weeks after the second dose) and long-term (12 weeks after vaccination) follow-ups in 62 CLL and 60 MM patients. Total anti-receptor binding domain (RBD) antibodies were detected in 22/60 (37%) MM patients before vaccination. This rate increased to 42/46 (91%) 2–5 weeks after the second dose, which remained stable with 44/47 (94%) positive patients 12 weeks after the second dose. Notably, they observed a tendency to higher frequencies of YLQ-specific CD8+ T cells a short time after the second dose compared to baseline (median: 0.18 vs. 0.11, $p < 0.06$), which might confirm the induction of specific CD8+ T cells after vaccination. In the CLL cohort, total antibody response was detectable in 13/62 (21%) of patients before vaccination. However, this increased to 18/40 (45%) 2–5 weeks after the second dose, with an additional increase to 30/42 (71%) 12 weeks after the second dose. However, in the CLL cohort, they did not find any differences between frequencies of YLQPRTFL-specific CD8+ T cells in either the short-term nor the long-term follow-up after the second dose compared to baseline samples.

Therefore, the authors suggested that specific CD8+ T cells against SARS-CoV-2 might be induced by vaccination, but do not correlate positively with serological responses.

COVID-19 in multiple myeloma

It has been shown that the risk of severe COVID-19 in multiple myeloma (MM) patients is significant. In a cohort of 617 MM patients, c. 34% died after a COVID-19 diagnosis [44]. In addition, the fatality rate in hospitalized patients increased from 31% to c.80% in patients with invasive ventilation. Furthermore, it was revealed that age represents another risk factor of COVID-19. The higher the age, the higher the probability of death. It was shown that 60-year-old patients have a c.31% probability of death, whereas in 80-year-old patients this is almost 50%. Interestingly, they proved that the time from diagnosis, and the number of prior types of treatment, are irrelevant as risk factors of COVID-19 disease.

Similarly, out of a group of 100 MM patients with COVID-19, 74% required hospital admission [45]. Among those hospitalized, 18% (13/74) needed mechanical ventilation, and 24% (18/74) unfortunately died. The laboratory findings in this multiple myeloma cohort revealed lymphopenia and elevated C-reactive protein, ferritin, D-dimer, and interleukin 6 (IL-6) levels. They found that the strongest risk factors for severe outcomes were similar to those in the general population i.e. hypertension and diabetes. However, the mortality rate was higher in the MM cohort compared to officially reported mortality rates.

One way to shield MM patients from severe COVID-19 or death caused by COVID-19 is vaccination. Researchers from all over the world have assessed immune responses after vaccination and their efficacy in MM. One of the first reports assessed the response to the first vaccination against SARS-CoV-2 in patients with MM. It was proved that 56% of patients (52/93) had anti-SARS-CoV-2 IgG in their blood after the first dose of the COVID-19 vaccine (BNT162b2 or mRNA-1273) [46]. Additionally, positive antibody results after the first vaccination, either IgG or total or both, were seen in 70% of patients (65/93). However, the total antibody assay provided a positive result in 30% (8/27) of patients with stable or progressive disease, and 48% (32/66) of patients under treatment. Therefore these authors suggested avoiding vaccination on a day when patients were receiving anti-myeloma therapy (except immunomodulatory agents) and that active disease might play a major role in attenuating the vaccine effect. However, in all cases where

the therapy cannot be postponed, the International Myeloma Society recommends vaccination.

An evaluation of the safety and antibody response was conducted following a two-dose SARS-CoV-2 messenger RNA vaccination in a group of 44 patients diagnosed with MM [47]. Half (22/44) of the patients received the BNT162b2 vaccine and the other half (22/44) received the mRNA-1273 vaccine. 93% (41/44) of patients had detectable antibody. Moreover, the three patients who had undetectable antibody (antibody titer < 0.79 U/mL) were treated with teclistamab and lenalidomide/ixazomib. Despite the limitation of the small size of cohort, the researchers stated that vaccination against SARS-CoV-2 is safe for patients with MM, and leads to high rates of seroconversion. Furthermore, increased anti-receptor binding domain (anti-RBD) antibody levels suggest that vaccination may indeed decrease COVID-19 morbidity and mortality in this population.

Currently, researchers are also exploring the impact of therapy on the efficacy of vaccines. Highly variable antibody responses to two doses of COVID-19 RNA vaccination were observed between MM patients during therapy and patients without therapy [44, 48]. The researchers tested 320 patients who received BNT162b2 or mRNA-1273 vaccinations and showed that patients who received therapy had a lower antibody level (70 U/mL) compared to patients without treatment (183 U/mL) [48]. Specifically, they observed that anti-CD38 and BCMA-targeted treatment is associated with lower antibody levels after vaccination. The negative effect of anti-CD38 therapy was also observed by Henriquez et al. [49]. They analyzed 72 MM patients: 66% (48/72) of them were on anti-CD38 treatment. They subsequently discovered lower IgG and similar IgA levels in patients on anti-CD38 treatment compared to other types of therapy. They also proved that BNT162b2 vaccine allowed patients to develop neutralizing antibodies (Nabs) against the alpha (51%) and delta (41%) COVID-19 variants. Although anti-CD38 therapy reduced the production of Nabs against the alpha variant compared to patients without treatment, there was no significant difference against the delta variant compared to other patients. The researchers suggested that impaired immune response to SARS-CoV-2 vaccine was favored by targeting nonmalignant B cells (e.g. anti-CD20 antibodies). Moreover, they suggested that impaired vaccine response in patients receiving anti-CD38 could have clinical implications that should be investigated prospectively.

Furthermore, two cohorts, each consisting of 35 patients, were examined [50]. The first group comprised individuals with both COVID-19 and MM, while the second group consisted of MM patients who had received the BNT162b2 vaccine. The researchers noted that patients on therapy in the first group had higher antibodies level (88%) compared to vaccinated patients (35.4%). On the other hand, patients without anti-myeloma treatment did not differ from the group of patients with COVID-19 in terms of their humoral response. Additionally, a highly significant difference in antibodies level was observed only in the vaccinated group. Patients without treatment had 91.7%, whereas those on therapy had 35.4%. Therefore, they suggested the administration of booster doses of vaccine to patients on therapy without prior COVID-19.

Another study confirmed that the response after either the BNT162b2 or the AZD1222 vaccine was dependent on vaccine-therapy interaction. It was proved that 53.5% (114/213) of MM patients developed measurable Nab after vaccination [51]. 20% (23/114) of patients were in remission, and 80% (91/114) were undergoing therapy. 50 days after vaccination, patients without anti-myeloma treatment reached a higher immune response (66%) compared to patients on belantamab mafodotin combinations (28.2%) or anti-CD38 combinations (48%). Furthermore, the antibodies level in the remaining types of treatment (62.8%) was similar to the antibodies level in patients without treatment (64.6%). Hence, patients during treatment should receive booster doses of vaccine.

COVID-19 in acute myeloid leukemia

A total of 108 patients with acute myeloid leukemia (AML) were analyzed to determine the clinical outcomes and assess the impact of therapeutic approaches during the COVID-19 infection [52]. 51.9% of patients had active leukemia and 70.4% were under any anti-leukemic treatment. It was shown that the main signs and symptoms of SARS-CoV-2 infection in AML patients include fever (75.0%), pneumonia (70.4%), cough (63.0%), dyspnea (51.9%), diarrhea (22.2%), nausea and/or vomiting (13.0%), rhinorrhea (13.9%), and headache (10.4%). Nevertheless, 38.9% of patients had severe outcome of the disease, while 3.7% of patients were asymptomatic. Therefore, 82.4% of patients received anti-SARS-CoV2 treatment: chloroquine or hydroxychloroquine (80.6%), lopinavir/ritonavir (50.2%), corticosteroids (37.0%), azithromycin (34.3%), tocilizumab (14.8%), plasma convalescent (2.8%), clinical trial medication (2.8%), remdesivir (1.9%), and/or anakinra (0.9%). Overall mortality was 43.5%. Higher mortality was observed in patients aged > 60 years (49.3%), male patients (56.1%), and those with active disease (60.4%) ($p = 0.036$, $p = 0.047$, $p = 0.014$). However, the researchers highlighted the protective effect of azithromycin ($p = 0.039$) and lopinavir/ritonavir ($p = 0.039$). They stated that AML patients are at a high risk of severe disease and increased mortality. It is recommended to delay therapy until SARS-CoV-2 is negative.

In research conducted by Marchesi et al. [53], 388 AML patients were examined. COVID-19 was severe in 41.2% and critical in 21.1% of patients. The mortality rate in patients with ongoing or recently treated AML was significantly higher compared to patients receiving treatment up to

three months or earlier before their diagnosis of COVID-19 ($p < 0.001$). Discontinuation of the chemotherapy which had been given within the month before the COVID-19 diagnosis was also associated with a higher mortality rate (80.9%). However, a significantly lower mortality rate was observed in patients whose chemotherapy was delayed (18.4%) compared to patients whose chemotherapy was not delayed (37.5%). Hence, it is suggested to delay AML treatment if possible to increase survival.

Recent studies have evaluated the effectiveness of COVID-19 vaccinations in AML patients. The antibody response to mRNA-1273 and BNT162b2 vaccines was evaluated in over 1,400 patients with hematological malignancies, including 34 with AML [54]. A positive antibody response was observed in 91.2% of AML patients.

Similar outcomes were observed in 46 AML patients [55]. In a cohort, 35 patients received the BNT162b2 vaccine and 11 patients the mRNA-1273 vaccine. The overall antibody response was 94.7%. Moreover, there was no significant difference between the antibody levels in healthy controls and AML patients in complete remission (CR) off therapy [1,079.0 (661.0–1,526.0) vs. 576.0 (158.3–1,708.8) U/mL, $p = 0.0885$]. However, AML patients receiving active treatment had lower antibody levels than those observed without treatment [92.2 (37.5–216.3) vs. 1,630.0 (806.0–2,454.0) U/mL, $p < 0.0001$]. Therefore, the researchers suggest that AML patients under observation without treatment in CR can be expected to have a vaccine effect comparable to that in healthy individuals.

COVID-19 in myelodysplastic syndrome

Myelodysplastic syndrome (MDS) is commonly associated with various infections e.g. COVID-19 which can lead to death [56, 57]. It has been proved that MDS patients have an increased mortality rate due to COVID-19 infection compared to the non-MDS population (42–50% vs. 29%) [53, 56–59]. High-risk MDS patients have the worst clinical outcome and the highest mortality rate, probably due to treatment with demethylating agents. Therefore, vaccination is recommended in this group of patients.

Recent studies have evaluated the effectiveness of COVID-19 vaccines in MDS [37, 60–63]. The antibody response after two doses of BNT162b2 vaccine was analyzed in MDS patients [60]. RBD-IgG antibodies were detected in 26/43 patients (60.5%) with MDS. However, Fattizzo et al. [61] observed increased antibody response in 45/46 (98%) low risk-MDS patients. Patients received either one dose of BNT162b2 or mRNA-1273. The researchers suggested that low risk-MDS patients have a seroconversion rate comparable to healthy individuals.

Experiments have revealed significantly reduced neutralization titers in MDS/AML patients following two or three doses of the BNT162b2 or mRNA-1273 vaccine, with geometric mean titer (GMT) of 1:139 against the homologous WA1/2020 strain compared to healthy controls (GMT) of 1:1,713 after second dose of vaccine [62]. Notably, in 11 patients who received a booster dose, WA1/2020 neutralizing antibodies were highly variable (GMT, 1:304), with 2/11 showing no neutralizing response and only 4/11 a strong response >1:500 GMT. Almost all patients with myeloid neoplasms showed minimal or no neutralizing antibodies against variants including omicron (92% of patients with <1:20 GMT against omicron) after two doses of vaccine. In addition, 63% of patients who received a booster dose showed significantly lower neutralization responses to all variants and no neutralization titer to omicron compared to healthy controls. Myeloid patients who received a booster dose showed increased antibody titers against omicron RBD, but lower than healthy adults (1,621 vs. 16,519 RBD IgG). Therefore, it is suggested to recommend booster doses to myeloid patients.

The efficacy of BNT162b2 and ChAdOx1 vaccinations was evaluated in a cohort of 38 patients diagnosed with MDS [37]. Antibody response after the second dose was 100% (15/15) in a BNT162b2 cohort and 76.2% (16/21) in a ChAdOx1 group. The researchers also evaluated T-cell response. The SARS-CoV-2 specific IFNg T-cell responses against the δ variant were present in 95% (20/21) of healthy adults, MDS ChAdOx1 70.6% (12/17), and MDS BNT162b2 71.4% (10/14). Notably, both serological and T-cell response was observed in 95% (20/21) of healthy adults, 71.4% (10/14) MDS BNT162b2, and 52.9% (9/17) MDS ChAdOx1. Therefore, BNT162b2 mRNA vaccine is recommended to increase both serological and T-cell response.

Recent studies have evaluated the effectiveness of antiviral drugs [63]. Research was conducted to assess the efficacy of molnupiravir (MOL), one of the first oral antiviral drugs to show significant benefits in reducing COVID-19 hospitalizations and deaths in healthy populations [64]. MOL was prescribed to patients with recent onset of symptoms (≤5 days), who did not require oxygen supplementation or hospitalization, and who were at high risk of disease progression to more severe COVID-19. They observed 59 MDS/AML patients and showed that only 20% of patients required hospitalization during MOL therapy. Nevertheless, they observed that mortality rate and hospitalization among hematological patients were still higher compared to a healthy population in terms of MOL therapy.

COVID-19 in diffuse large B-cell lymphoma

Recent studies confirmed that lymphoproliferative disorders e.g. non-Hodgkin lymphoma (NHL) are associated with a higher risk of COVID-19 infection [20, 39]. It has been proved that NHL patients have an increased mortality rate (31.8%) due to COVID-19 prior to vaccination. Therefore,

recent studies have evaluated antibody and mortality rates following vaccination in NHL patients.

A low neutralizing antibody (Nab) response has been observed in NHL patients after the first dose of the BNT162b2 and AZD1222 vaccines [65]. The study included six NHL patients vaccinated with BNT162b2 and two vaccinated with AZD1222. After the first dose of the vaccine, on day 22 post vaccination patients had lower Nab levels compared to controls (17% vs. 32%). Despite the low response, this suggests a booster dose in NHL patients, particularly those with a suboptimal response.

Perry et al. [66] analyzed the effect of anti-lymphoma therapy on the effectiveness of two doses of BNT162b2 vaccination in 149 B-NHL patients, including 69 diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBL). 28 patients (19%) were treatment-naïve, 55 (37%) were being actively treated with rituximab/obinutuzumab (R/Obi) (monotherapy or in combination), and 66 (44%) were last treated with R/Obi >6 months prior to vaccination. Antibody response was achieved in 73/149 (49%) B-NHL patients. However, a significantly lower antibody response (7.9%) was observed in patients treated with anti-CD20 Abs within six months prior to vaccination. Nevertheless, treatment-naïve patients and patients who completed therapy >6 months prior to vaccination had significantly higher seropositivity rates than actively treated patients (89.3%, 66.7% vs. 7.9% respectively). Thus the researchers stated that a longer time from exposure to anti-CD20 Abs is associated with higher seropositivity following BNT162b2 vaccination.

Antibody response was studied in 56 patients with Burkitt's lymphoma (BL), DLBCL and PMBL combined following BNT162b2, mRNA-1273 or Ad26.COV2-S vaccine [67]. 51% (28/55) of patients seroconverted after the first dose of vaccine, although in those who received an additional dose the seroconversion rate was 100% (10/10). Hence, booster doses are recommended.

Moreover, humoral response following booster BNT162b2 vaccination was evaluated in patients with B-cell malignancies by Terpos et al. [68], who observed 54 NHL patients and found that one month after the third dose, Nabs levels were very high in all healthy participants (median 97.5%), while in the NHL group half of the patients had Nabs levels below 20%. In addition, there were 32 patients (59.3%), with Nabs levels less than 30% and only 35.3% of patients with Nab ≥50% after the third dose. Terpos et al. observed that anticancer treatment is related to lower Nabs levels. Rituximab-treated NHL patients did not increase Nabs (16% before the third dose vs. 19% one month after the third dose) compared to NHL patients not treated with rituximab who experienced a statistically significant increase in Nabs (71.4% after the third dose vs. 44% before the third dose). Therefore, the researchers suggested to delay therapy, if possible.

Another study identified seroconversion rates after the third dose of BNT162b2 vaccine was evaluated in 44 patients with B-cell non-Hodgkin lymphoma (B-NHL), including 16 with DLBCL, who had not responded to two previous doses [69]. The overall seroconversion rate was 29.5% (13/44). However, in patients previously treated with anti-CD20 moAb who had completed treatment six months or more prior to the booster dose, the seroconversion rate was significantly higher at 47.8% (11/23) compared to 10.5% (2/19) of patients treated with anti-CD20 moAb within the six months prior to the booster (p = 0.019). Notably, 50% (8/16) of DLBCL patients were serologically positive after booster vaccination compared to 17.9% (5/28) of patients with another B-NHL (p = 0.025). The authors recommend booster doses of BNT162b2 vaccine for those patients who fail to seroconvert following two doses of vaccine.

COVID-19 in chronic myeloid leukemia

Research demonstrated that the rate of COVID-19 infection among chronic myeloid leukemia (CML) patients in Italy was exceptionally low one year into the pandemic [70]. In a cohort of 8,665 CML patients, they recorded 217 SARS-CoV-2-positive patients (2.5%). 21 patients (9.6%) required hospitalization, whereas 18 (8.2%) required respiratory assistance, eight (3.6%) were admitted to an ICU, while 170 (78%) were merely quarantined. Moreover, 12 patients died due to COVID-19, with a mortality rate of 5.5% in a COVID-19 positive cohort and 0.13% in the whole cohort of CML patients. The authors stated that the mortality rate in CML appears lower compared to other hematological malignancies, and that most patients were completely asymptomatic. They also highlighted the potential positive role of tyrosine kinase inhibitor (TKi) therapy in decreasing COVID-19 occurrence and mortality.

The outcome of COVID-19 was analyzed in 551 patients with CML receiving TKi [71]. 346 (65%) of them received imatinib, 102 (19%) dasatinib, 59 (11%) nilotinib, and 44 (8%) other types of TKi therapy. All 530 were in the CP stage. 81 (15%) had a complete hematological response (CHR), 52 (10%) a complete cytogenetic response (CCyR), and 387 (73%) a major molecular response (MMR). Five patients (0.9%) were diagnosed with COVID-19. The researchers observed that 1/21 patients receiving a third generation TKI (ponatinib and HQP1351) developed COVID-19 versus 3/346 patients receiving imatinib versus 0/162 patients receiving second generation TKIs (p = 0.096). They suggested that persons receiving TKI therapy may have a higher likelihood of developing COVID-19 than the general population, although the absolute case numbers are very low and clinical features are as normal.

Ali et al. [72] identified SARS-CoV-2 omicron variant infection in patients with CML. 11 patients had a mild disease. They suggested that infection with the omicron

variant usually results in mild disease not requiring hospitalization in patients with CML.

Many studies have evaluated the effectiveness of COVID-19 vaccinations, which are recommended for CML patients as immunocompetent individuals who are in a high-risk group for severe disease. Factors associated with negative antibody response after COVID-19 vaccination were analyzed in patients with hematological diseases [73]. Vaccination was performed with BNT162b2, mRNA-1273, ChADOx1, or a combination. Notably, in a cohort of CML patients, 100/101 (99%) had a positive vaccine response. Hence, the authors suggested that patients with CML were significantly less likely to have a negative response in univariate analysis. These patients were on TKI treatment or in treatment-free remission.

Humoral responses after a second anti-SARS-CoV-2 vaccine dose were studied in 54 patients with CML treated with TKi [74]. Approximately 21 days after the first dose of either BNT162b2 or ChAdOx1, 48/50 CML patients (96%) and 25/26 healthy persons (96%) had seroconverted. However, seropositivity declined c.50 days after the first dose in CML patients (31/39, 79.5%), but not in healthy persons (25/27, 92.6%). Then, c.21 days after the second dose, 51/52 patients (98%) and 29/29 healthy persons (100%) were seropositive, a finding that persisted up to c. 50 days after the second dose of vaccination.

The authors stated that patients with CML on TKI are able to develop an antibody response against SARS-CoV-2 that is not significantly different from that seen in healthy persons, and that persists for at least three months after the second dose of vaccine.

Similarly, humoral and poly-functional T-cell responses were analyzed in patients with CML after a single dose of BNT162b2 mRNA vaccine [75]. In a cohort of 16 patients, a positive anti-S IgG ELISA response was seen in 87.5% (14/16). Nonetheless, T-cell response was seen in 93.3% (14/15) of evaluable patients. A polyfunctional cytokine response in either $CD4^+$ or $CD8^+$ T cells was seen in 80% (12/15) of patients, with a poly-functional $CD4^+$ response (with expression of IFN-γ, TNF-α or IL-2) in 60% (9/15) and a poly-functional $CD8^+$ T-cell response in 40% (6/15) Notably, the only patient not showing a T-cell response was after allo-HSCT and was taking ponatinib. Therefore, the researchers showed that a single dose of BNT162b2 vaccine demonstrated the immunogenicity in most patients with CML with both humoral and poly-functional T-cell responses compared to patients with lymphoid malignancies.

Despite the large number of studies on vaccine response, little is known about the safety of vaccination in CML patients. Therefore, 335 CML patients were recruited who were vaccinated against SARS-CoV-2 with CoronaVac (164), BBIBP-CorV (91), ZF2001 (5), and others (75) [76]. A total of 19.1% (64/335) respondents reported adverse events (AEs) after vaccination. The most common (11%, 37/335) AE was pain at injection site. However, fatigue (3%, 10/335), sleepiness (2%, 7/335) and flu-like symptoms (2%, 7/335) were regarded as systemic AEs. Moreover, the AEs of vaccination were not significantly associated with vaccine brand or TKI type. Hence, the researchers suggested that the SARS-CoV-2 vaccines described in the study are safe for CP-CML patients.

Although patients with CML exhibit a higher rate of seroconversion compared to individuals with other hematological malignancies, they are still at risk of developing breakthrough infections. 287 fully vaccinated (BNT162b2, mRNA-1273 or Ad26.COV2.S) patients with CML were recruited, and the researchers observed that those patients had the highest risk for breakthrough infections (17.4%) among the seven hematological malignancy types compared to the healthy population (4.5%) [30]. Additionally, the authors suggested that breakthrough infections in hematological patients were associated with significant clinical outcomes, including hospitalizations and mortality.

COVID-19 treatment in hematological patients

Treatment of COVID-19 in patients with hematological malignancies depends on the stage of the disease, the patient's condition, and the type of anti-cancer treatment used. Prior to vaccination for mild symptoms of COVID-19 such as fever, cough and muscle aches, patients were advised to continue to isolate at home and to follow hygiene and social distancing guidelines. For more severe symptoms, such as shortness of breath and low blood oxygen levels, hospitalization was required [77].

Patients with hematological malignancies with an inadequate response to vaccination required other protective measures to prevent or minimize the risk of breakthrough infections, including antiviral therapy such as remdesivir, and anti-inflammatory drugs such as corticosteroids, to reduce inflammation caused by COVID-19, including ventilation, oxygen, monoclonal antibody therapy, immunomodulators or convalescent plasma [78–81].

The effectiveness of convalescent plasma (CP) was assessed in 3,596 patients, demonstrating its positive impact on the clinical outcomes of COVID-19 treatment. Notably, the early administration of CP was shown to reduce the duration of hospitalization (overall 13 vs. 12 days $p \leq 0.001$) [81].

The 2021 European Conference on Infections in Leukemia (ECIL 9) recommended in unvaccinated patients at risk of severe COVID-19 or COVID-19 progression, pre-exposure prophylaxis with long-acting anti-SARS-CoV-2 monoclonal antibodies (bamlanivimab/etesevimab, casirivimab-imdevimab, sotrovimab) [22]. In patients with mild COVID-19, molnupiravir or remdesivir or nirmatrelvir + ritonavir or monoclonal antibody were recommended. Nirmatrelvir/

/ritonavir has been shown to reduce the number of hospitalizations or deaths by 89% compared to a placebo in high-risk patients treated within three days of onset of COVID-19-related symptoms [82]. Remdesivir showed a similar reduction in hospitalizations and deaths of 87% in non-hospitalized patients, including a small group of 23 (4.1%) patients with impaired immune system [83]. During a clinical trial, molnupiravir showed a relative 30% reduction in the risk of hospitalization or death [84]. Hence, it has been recommended to use in hematological patients who do not require supplemental oxygen.

In patients with moderate or severe COVID-19, remdesivir and dexamethasone have been recommended. Dexamethasone was recommended in patients who required oxygen therapy and who had increased inflammatory markers. During a clinical trial, 6 mg daily for 10 days of dexamethasone showed a 3% reduction in mortality in patients on oxygen therapy [85]. Nevertheless, some potentially therapeutic agents have not shown a benefit in COVID-19 patients, including azithromycin, hydroxychloroquine, lopinavir-ritonavir, and convalescent plasma [86].

The results of early treatment of SARS-CoV-2 infection were evaluated in 328 hematological patients treated with monoclonal antibodies (MABs) (n = 120, 37%; sotrovimab, n = 73) or antivirals (n = 208, 63%; nirmatrelvir/ritonavir, n = 116, remdesivir n = 59, molnupiravir n = 33) [87]. Univariate and multivariate analysis confirmed a higher risk of failure and longer virus shedding in patients treated with MABs compared to those treated with antivirals.

Despite the existence of many forms of anti-COVID-19 therapy, vaccination is still the most effective in terms of reducing mortality and morbidity [87].

Conclusions

Patients with hematological malignancies are at high risk of severe COVID-19 due to disease-related, as well as treatment-related, immunosuppression, older age, and other comorbidities [88]. Treatment of COVID-19 in patients with hematological malignancies includes antiviral therapy, anti-inflammatory drugs, monoclonal antibody therapy, and/ /or immunomodulators. Treatment depends on the stage of the disease, the patient's condition, and the type of anti-cancer treatment used [78–80]. Infection prevention methods are recommended, although serological response following vaccination varies according to the hematological malignancy subtype, with better responses seen in CML, AML, and low risk MDS, while poorer responses have been seen in patients with CLL and lymphoma patients [20, 89, 90]. Hematological patients have a decreased likelihood of developing antibody response compared not only to the healthy population but also to patients with solid tumors [91]. Furthermore, patients actively treated with BTKis, CAR-T, ruxolitinib, venetoclax, anti-CD20 or anti-CD38 antibody treatments seem to experience a significant reduction in their ability to mount an effective immune response to vaccination. This could potentially leave them vulnerable to SARS-CoV-2 infection without adequate protection [29].

Therefore, a new approach is urgently needed to treat high-risk patients who respond poorly to vaccines and develop only limited protection from the infection. This group of patients requires other protective measures to prevent or minimize the risk of breakthrough infections including antiviral therapy such as remdesivir and anti-inflammatory drugs such as corticosteroids to reduce inflammation, as well as monoclonal antibody therapy or immunomodulatory drugs [78–80]. Importantly, patients with a history of SCT, COVID-19, CML, CMPDs, TKi, infection prior to vaccination, or no active treatment during vaccination, have been associated with increased seroconversion [18]. It has been proved that patients with myeloid malignancies have a seroconversion rate comparable to that of the healthy population after the mRNA-1273 or BNT162b2 vaccine. Moreover, the American Society of Transplantation and Cellular Therapy has advised that COVID-19 vaccines should be offered to patients three months or later following SCT and CAR-T therapy [89, 92].

Our research focused mainly on the use of mRNA vaccines including mRNA-1273 or BNT162b2, and therefore additional studies characterizing other vaccine platforms are required due to potentially different seroconversion. There is still limited data about the evaluation of the T-cell response, and hence further studies are recommended to assess T-cell responses post-vaccination and to estimate the effects of SARS-CoV-2 booster doses to make recommendations for COVID-19 vaccination in patients with hematological malignancies [91].

There is a need for more extended studies that will shed light on the causes behind the absence of a response to vaccines, how patients who have developed an antibody response can sustain it over time, and the use of booster doses in non-responders, particularly in the case of CLL patients who are actively receiving treatment at the time of vaccination and have a recent history of using anti-CD20 monoclonal antibodies.

Toll-like receptors (TLRs) detect the presence of SARS--CoV-2. Subsequently, downstream transcription factors like IRFs are stimulated, leading to generation of interferon type I (IFN-I) and excessive inflammation. In response to SARS-CoV-2 infection, immune system becomes activated, leading to engagement of various immune cells. Simultaneously, NF-κB is activated, prompting synthesis of pro-inflammatory cytokines known as 'cytokine storm'. These pro-inflammatory cytokines further trigger JAK-STAT or NF-κB signaling pathways by binding to their receptors on immune cells, resulting in increased expression of pro-inflammatory genes and eventually leading to multiorgan failure or death [6, 95–98].

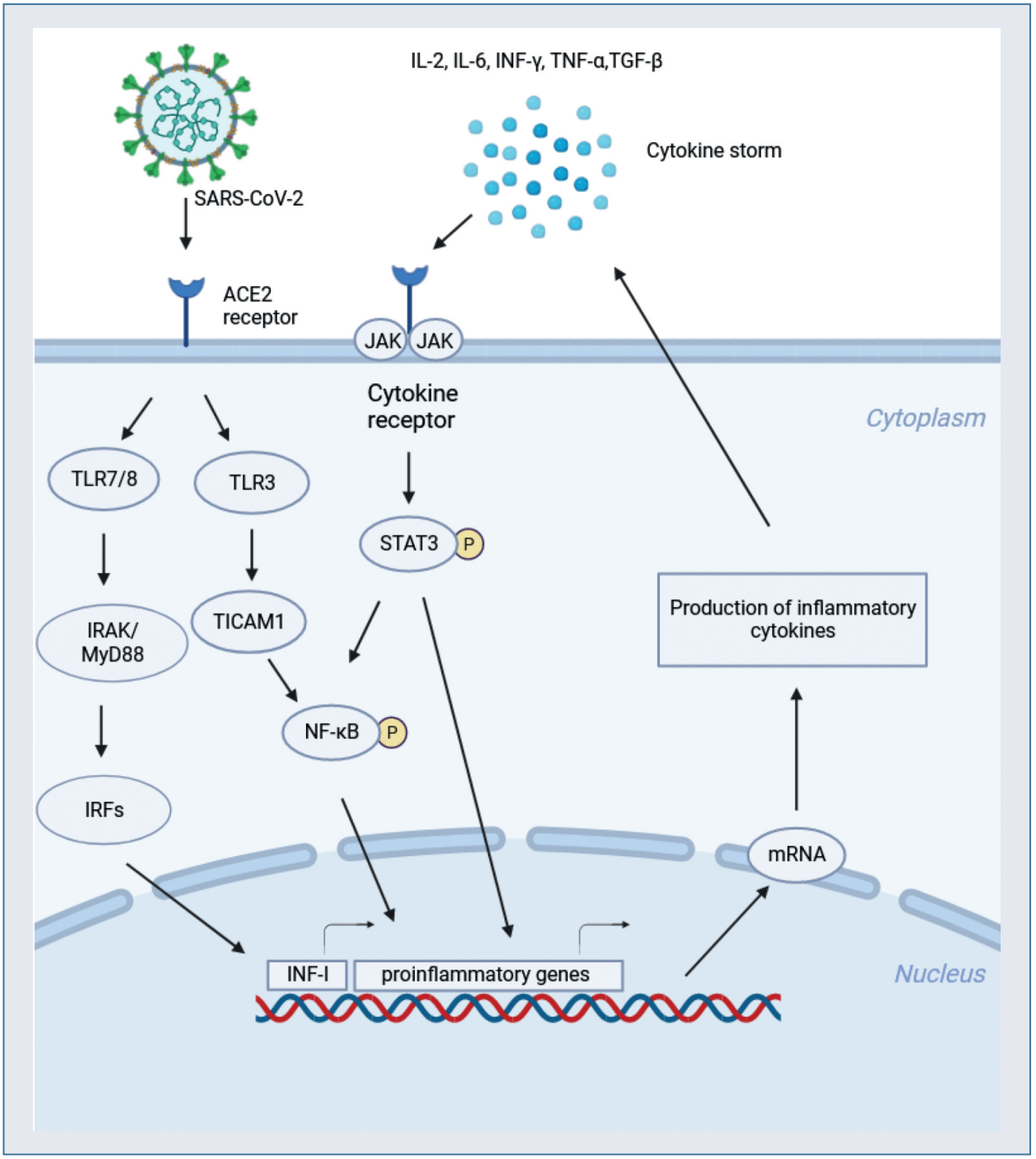

Figure 1. Signaling pathways responsible for triggering a cytokine storm in individuals infected with COVID-19 [64, 93–95]. Created with BioRender.com; LR — Toll-like receptors; ACE2 — angiotensin converting enzyme-2; IL — interleukin; IFN — interferon; JAK — Janus kinase; STAT3 — signal transducer and activator of transcription protein 3; NF-κB — nuclear factor kappa B; TICAM1 — TIR domain containing adaptor molecule 1; IRAK/MyD88 — myeloid differentiation primary response 88; IRFs — interferon regulatory factors; TNF-α — tumor necrosis factor α; TGF-β — transforming growth factor β

Table I. Efficacy of different COVID-19 vaccines in patients with hematological malignancies with lower response risk factor

Vaccine	N	Doses	Type of neoplasm	Median age	Overall response	Risk factors of lower response	Control group	Adverse events	Study
BNT162b2 (n = 48) ChAdOx1 (n = 45)	93	1	MM	65 (positive) 70 (negative)	56% (anti-SARS-CoV-2 IgG) 70% (total antibody)	1. Therapy at time of vaccination 2. Stable disease or progressive disease	Not reported	Not reported	Bird et al. [46]
BNT162b2 (n = 22) mRNA-1273 (n = 22)	44	1, 2	MM	64	93% (on therapy) 94% (not on therapy)	Not reported	Not reported	Pain at injection site, fatigue, headache	Greenberg et al. [47]
BNT162b2 (n = 221) mRNA-1273 (n = 87) Unknown (n = 12)	320	1, 2	MM	68	84.2% (219/260) 18.8% (60/320) had COVID-19 prior to immunization, hence were excluded	1. Anti-CD38 therapy 2. BCMA-targeted therapy	67 healthcare workers	Not reported	Oekelen et al. [48]
BNT162b2 (n = 72)	72	1, 2, 3 (only patients on anti-CD38 therapy)	MM	69.86	44% (1 month after D1) 85% (3 months after D1) 51% and 41% response against alpha and delta variants, respectively	1. Anti-CD38 therapy	23 healthy volunteers	Not reported	Henriquez et al. [49]
BNT162b2 (n = 215) ChAdOx1 (n = 61)	213	1, 2 (BNT162b2) 1 (ChAdOx1)	MM	74	62.8% Nab titers ≥30% 57.3% Nab titers ≥50% 4 weeks after D2 of BNT162b2 vaccine or 7 weeks after D1 of ChAdOx1	1. Anti-CD38 therapy 2. Belantamab-mafodotin combination	226 healthy controls	Pain at injection site, erythema and/or swelling after ChAdOx1, fatigue, fever, muscle pain, headache after BNT162b2	Terpos et al. [51]
BNT162b2 (n = 35) (35 vaccinated and other 35 with COVID-19 without vaccine)	70	1, 2	MM	65	87.6% Nab for COVID-19 positive 58.7% for vaccinated patients	1. Active anti-myeloma treatment only among vaccinated patients	35 matched fully vaccinated patients	Not reported	Gavriatopoulou et al. [50]
BNT162b2 (n = 35) mRNA-1273 (n = 11)	46	1	AML	67.5	94.7%	1. Active anti-myeloma treatment	43 healthy controls	Not reported	Mori et al. [55]

Table I (cont.). Efficacy of different COVID-19 vaccines in patients with hematological malignancies with lower response risk factor

Vaccine	N	Doses	Type of neoplasm	Median age	Overall response	Risk factors of lower response	Control group	Adverse events	Study
BNT162b2 (n = 149) B-NHL including 69 DLBCL patients)	149	1, 2	DLBCL	64	49% overall response 7.9% patients treated with anti-CD20 Abs within 6 months prior to vaccination	1. Anti-CD20 Abs within 6 months prior to vaccination	65 healthy controls	Pain at injection site, tiredness, muscle pain	Perry et al. [66]
BNT162b2 (n = 16) ChAdOx1 (n = 22)	38	1, 2	MDS	67.5	Humoral response 100% BNT162b2 76.2% ChAdOx1 T-cell response BNT162b2 71.4% ChAdOx1 70.6% Both responses 71.4% BNT162b2 52.9% ChAdOx1	Not reported	30 healthcare workers	Not reported	Abdul-Jawad et al. [37]
BNT162b2 mRNA-1273 Ad26.COV2.S	36	1, 2	CLL	62	60% not on therapy 72% treatment naïve 33% in patients on BTKi therapy	1. BTKi therapy 2. Adenovirus vaccine	Not reported	Not reported	Haydu et al. [35]
BNT162b2	167	1, 2	CLL	71	39.5%	1. On CLL therapy 2. BTK inhibitors and venetoclax ± anti-CD20 antibody	52 healthy controls	Pain at injection site, local erythema or swelling	Herishanu et al. [99]
BNT162b2	172	3	CLL	72.1	23.8%	1. On CLL therapy 2. BTK inhibitors and venetoclax ± anti-CD20 antibody	Not reported	Pain at injection site, local erythema, swelling, fatigue	Herishanu et al. [38]
BNT162b2	61	1, 2	CLL	69.4	90.2% Six months after D2	1. Active CLL treatment	39 healthy controls	Not reported	Herishanu et al. [100]

Table I (cont.). Efficacy of different COVID-19 vaccines in patients with hematological malignancies with lower response risk factor

Vaccine	N	Doses	Type of neoplasm	Median age	Overall response	Risk factors of lower response	Control group	Adverse events	Study
BNT162b2 (n = 204) ChAdOx1 (n = 296)	500	1, 2	CLL	67	67%	1. BTKi therapy 2. Male gender 3. IgA or IgM hypogammaglobulinemia	93 healthy donor controls	Not reported	Parry et al. [40]
BNT162b2 (n = 377) mRNA-1273 (n = 76) Unknown (n = 77)	530	1, 2, 3	CLL	71	27% after D1 52% after D2 35% after D3 in post-dose 2 seronegative patients	1. BTKi therapy 2. BTKI in combination with anti-CD20 monoclonal antibodies or venetoclax 3. Over 65 years	Not reported	Not reported	Bagacean et al. [41]
BNT162b2 ChAdOx1	50	1, 2	CML	51.2	96% 21 days after D1 79.5% 50 days after D1 98% 21 days after D2	Not reported	31 healthy controls	Not reported	Claudiani et al. [74]
BNT162b2	43	1, 2	MDS	73.0	60.5%	Not reported	272 healthy controls	Pain at injection site, fatigue and headache	Rahav et al. [60]
BNT162b2, mRNA--1273, ChADOx1	101	1, 2	CML	64	99%	Patient who did not seroconvert received combined treatment with ruxolitinib and bosutinib	35 patients with autoimmune and benign diseases	Not reported	Rotterdam et al. [73]
BNT162b2, mRNA-1273	62	1, 2	CMPDs	71.9	57.7 % MF 91.7% PV or ET	Patients receiving ruxolitinib	Not reported	Not reported	Cattaneo et al. [101]

MM — multiple myeloma; CLL — chronic lymphocytic leukemia; B-NHL — B-cell non-Hodgkin lymphoma; DLBCL — diffuse large B-cell lymphoma; AML — acute myeloid leukemia; CML — chronic myeloid leukemia; N — number of patients; D1 — first dose of vaccine; D2 — second dose of vaccine; D3 — third dose of vaccine; BTKi — Bruton's tyrosine kinase inhibitor; BCMA — B-cell maturation antigen; anti-CD20 Abs — anti-CD20 antibodies; MF — myelofibrosis; PV — polycythemia vera; ET — essential thrombocythemia; NS — not significant $p \geq 0.05$

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Supplementary material
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