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COVID-19 in Patients with Chronic Lymphocytic Leukemia: What Have We Learned?

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Abstract
Background: Chronic lymphocytic leukemia (CLL) is a prevalent hematological malignancy (HM) characterized by inherent immunodeficiency, which is further pronounced by disease-directed therapy. The COVID-19 pandemic has had devastating outcomes, and although its impact has diminished over time, it continues to be a cause of significant morbidity and mortality, particularly among immunodeficient patients. ***Summary:*** In this review, we describe mechanisms of immune dysfunction in CLL in relation to COVID-19, provide an overview of the clinical outcomes of the disease in this patient population, and identify risk factors associated with severe morbidity and mortality. Additionally, we acknowledge the influence of the rapidly evolving landscape of new disease variants. The review further delineates the humoral and cellular responses to vaccination and their clinical efficacy in preventing COVID-19 in CLL patients. Moreover, we explore potential approaches to enhance these immune responses. Pre- and post-exposure prophylaxis strategies are discussed, along with description of common agents in the treatment of the disease in both outpatient and inpatient setting. Throughout the review, we emphasize the interplay between novel therapies for CLL and COVID-19 outcomes, prevention, and treatment and describe the impact of COVID-19 on the utilization of these novel agents. This information has the potential to guide clinical decision making in the management CLL patients. ***Key Messages:*** CLL patients are at risk for severe COVID-19 infection. Vaccinations and COVID-19 directed therapy have improved outcomes in patients with CLL, yet clinical challenges persist.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and its associated coronavirus disease of 2019 (COVID-19) have had a severe global impact. Although it had gradually abated, it is still a cause of significant morbidity and mortality [1]. The course of COVID-19 infection can vary widely, ranging from asymptomatic infection [2] or mild disease, to critical illness characterized by respiratory failure, shock, and multiorgan failure [3]. Despite lower case fatality rates (CFR) in the unvaccinated population and the emergence of less pathogenic variants, the CFR remains significant in older adults (2.9% at age 70 according to one estimate [4]). Furthermore, CFR is considerably higher in

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hospitalized patients [5] and it may not fully capture the true burden of the pandemic in terms of excess mortality resulting from other conditions due to delayed care [6].

Risk factors for severe disease and death include age over 65 years and comorbidities, such as cardiovascular disease, lung disease, liver and kidney disease, obesity, and immunosuppression [7, 8]. While cancer has been identified as a potential risk factor for severe disease, a matched cohort study failed to demonstrate an excess risk among cancer patients [9]. However, a systematic review and meta-analysis of patients with HM demonstrated a high mortality rate in this specific patient group, with age over 65 years being the main risk factor. Interestingly, recent anti-cancer therapy did not show an association with increased mortality in this meta-analysis [10].

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) is the most common leukemia in the Western World [11] with a median age at diagnosis of about 70 years [12]. Consequently, this patient population often present with multiple risk factors for severe COVID-19 disease [13]. CLL is well-recognized for its inherent association with immune dysfunction. Patients with CLL commonly exhibit hypogammaglobulinemia, qualitative and quantitative B- and T-lymphocyte defects, reduced levels of CD4+ T-cells, and compromised innate immune responses. While immune dysfunction is already evident in early-stage CLL and treatment-naïve patients, it may further deteriorate with disease progression and therapy, rendering CLL patients particularly susceptible to infections, which are a significant source of morbidity and mortality [14].

SARS-CoV-2 has shown a remarkable ability to evade or delay the activation of intracellular innate immune responses (mediated by interferon), enabling the virus to replicate effectively. This highlights the crucial role of the adaptive immune system in containing the virus. Indeed, severe cases of COVID-19 have been linked to a delayed innate response, deficiency of specific CD4+ and CD8+ T cells and a delayed antibody response [15, 16]. As humoral and cellular immune responses act in concert to potentially impede virus entry and eliminate infected cells, respectively, it is of particular interest to examine the outcomes of COVID-19 in CLL patients.

COVID-19 Infection in CLL Patients

As of April 2023, there have been a staggering 680 million reported cases of COVID-19 worldwide, with over 6.8 million deaths [17]. The CFR stands at approximately 10%, although this figure has varied considerably over time, likely influenced by factors such as vaccination-induced immunity, prior infection, and variant evolution [18].

Determining whether the infectivity rate is increased among CLL patients is challenging. COVID-19 incidence rate among over 15,000 CLL patients from 47 centers in Italy was at 3.3%, which is similar to the general incidence rate in Italy one year after the pandemic break [19]. In a meta-analysis of reported studies, the estimated prevalence of COVID-19 in CLL patients was 0.6% [20]. Another report from Barcelona estimated COVID-19 prevalence among CLL patient at 0.95%, comparable to that of the general population [21]. However, it is important to note that many CLL patients have been living in isolation, especially during the initial waves of the pandemic, which probably led to an underestimation of the true infectivity rate [22]. This is supported by evidence of reduced non-coronavirus infections during isolation [23].

Two pivotal registries have provided insights into the outcomes of COVID-19 infection in patients with CLL. A retrospective study conducted by the European Research Initiative on CLL (ERIC) and the Italian CLL Campus, initially included 190 patients with positive PCR for COVID-19. Among them, 79% experienced severe disease. This was associated with advanced age (≥65 years), but there was no significant correlation with ongoing or recent anti-leukemic therapy. The mortality rate was 36.4% among patients with severe disease, compared to 2.6% among those with mild disease. Interestingly, age and comorbidities did not influence mortality [24]. An updated analysis of the cohort, which included 941 patients until March 2021, revealed a similar CFR in severe cases (38.4%), but worse OS was observed with increasing age, any CLL-directed therapy, and cardiac failure [25]. This serves as a noteworthy example of how our understating of the pandemic and associated risks has matured over time.

Another international retrospective study by Mato et al. [26] involved 198 patients, half of whom were from US centers. The median age was 70.5 years, and 90% required hospitalization. Thirty-nine percent were treatment naïve, 61% had received at least one line of therapy, and 45% were on active therapy at the time of COVID-19 diagnosis. The overall CFR was 33%. Treated patients showed similar rates of admissions, ICU admissions, and mortality. An updated analysis of this cohort, which included 374 patients, revealed an overall CFR of 28%. Seventy-five percent needed hospitalization, and 27% were admitted to the ICU. Risk factors associated with worse outcomes were age over 75 and CIRS

score greater than 6. Factors such as sex, hypogammaglobulinemia, and CLL-directed therapy were not significantly associated with survival. Additionally, the CFR was notably lower in the later cohort (May 2020 to February 2021) compared to the earlier cohort (February to April 2020), with rates of 20% and 40%, respectively, in hospitalized patients [27]. Similar findings have been reported by other registries [28–30], including a meta-analysis that evaluated mortality in hemato-oncology patients with COVID-19 infection, which indicated a mortality rate of 31% in CLL patients, similar to other HM [10].

The previously mentioned studies, although important, were relevant to the first waves of COVID-19, dominated by the alpha and delta strains. A more recent report from Denmark, highlighted that despite a 23% in-hospital 30-day mortality rate among CLL patients during the Omicron sub-lineage BA.2 surge, the rates of hospitalization and ICU admissions have significantly decreased. Consequently, the overall 30-day mortality in patients with CLL was 2% [31]. Other registries have also reported lower mortality rates in CLL patients during the Omicron era [32, 33]. The reduction in mortality rates may be attributed not only to lineage evolution, but also to the implementation of vaccines, other prophylactic measures, and improved supportive and COVID-specific care, which will be further discussed.

Interestingly, in the US retrospective study by Mato et al. [27] only 60% of patients had seroconversion after COVID-19 infection. The rate was lower in treated patients (48% on Bruton tyrosine kinase inhibitors (BTKi), 30% on venetoclax) compared to 74% in untreated patients. Somewhat better results were demonstrated in a smaller study, with 33 out of 40 patients (82%) showing seroconversion after infection, although most of the patients were either treatment-naïve or off-therapy. Notably, SARS-CoV-2-specific T-cells were detected in 14 out of 17 patients in this cohort [34]. This finding may be important, as it had been previously shown (although not specifically in CLL), that T-cells from convalescent donors retain significant response capabilities across variants of COVID-19 [35], in contrast to humoral response [36].

Prolonged COVID-19 infection is another concern in immunocompromised patients [37–39]. Several reports have highlighted cases of prolonged fever and/or pulmonary symptoms associated with ongoing active COVID-19 infection. Patients with HM are particularly susceptible to prolonged shedding of the virus. In one study, mean duration of positive PCR results in HM patients was 21.2 days compared to 7.4 in matched controls [39]. Another study found that patients with HM took nearly twice as long to achieve viral negativity [40]. Furthermore, there have been reports underscoring the occurrence of biphasic presentation of the disease in patients treated with anti-CD20 monoclonal antibodies (mAbs) [41]. In a study involving 328 patients with HM, mostly treated in the Omicron period, prolonged COVID-19 infection was evident in 9.5% of patients, and specifically 7.8% during the Omicron surge. Interestingly, fewer vaccine doses were associated with a higher rate of COVID-19 directed treatment failure [42].

Moreover, in the era of antiviral therapies, such as Nirmatrelvir/Ritonavir or Molnupiravir (as discussed later), a phenomenon of rebound COVID-19 infection was described. Tadmor et al. [43] reported on 18 CLL patients who experienced rebound disease, accounting for 5.4% of the CLL patients included in the study. Interestingly, the use of antiviral therapy and concurrent myeloproliferative disease were two independent factors associated with this phenomenon. Specifically, rebound rates were 9.8% among patients treated with Nirmatrelvir/Ritonavir or Molnupiravir and 3.8% in untreated patients. While the underlying mechanism remains unclear, it appears that the potential benefit of the drug outweighs the risk [44], at least in immunocompromised patients.

CLL Treatment during COVID-19 Infection

The impact of the pandemic on CLL-directed therapy has been a matter of significant concern. Considerations such as timing of therapy, route of administration, the need for close monitoring, and the risk of infections have all become crucial factors in the selection of appropriate treatment. The data presented here pertains exclusively to unvaccinated patients with CLL.

There is limited data available regarding the outcomes of COVID-19 in patients who have undergone chemoimmunotherapy (CIT) regimens for the treatment of CLL, which are no longer commonly used. In a retrospective study conducted in the Czech Republic, 26% of treated patients received CIT, and all of them had discontinued therapy due to COVID-19 infection. In this cohort, both CIT and any CLL-directed therapy were associated with increased mortality [28].

In the ERIC study [25], a third of the patients were treated for CLL during COVID-19 infection, more than a half of whom were on BTKi and 15% on venetoclax-based regimen. Interestingly, CLL treatment, and specifically BTKi, did not significantly impact the severity of

infection. Seventy percent of physicians chose to hold BTKi during infection. However, patients who continued BTKi did not demonstrate a significant improvement in outcomes compared to those who stopped treatment (p value = 0.08), and both groups fared worse than untreated patients.

BTKi were even considered as potential therapy for patients with COVID-19 infection, based on reports on elevated levels of BTK activity in blood monocytes from individuals with severe COVID-19. Several small series have shown that administration of BTKi can reduce the duration of mechanical ventilation and mortality rate in hospitalized patients with severe COVID-19 [45–49]. For instance, the use of acalabrutinib in 19 hospitalized patients with severe COVID-19 resulted in improved oxygenation in the majority of cases. Another study demonstrated recovery in 6 out of 8 patients with severe COVID-19 after BTKi therapy. Possible mechanisms of action include reduced hyperinflammation, alteration of monocyte function, and attenuation of lymphopenia. However, the benefits of BTKi for the treatment of severe COVID-19 infection have not been yet established in prospective trials.

Venetoclax is a BCL2 inhibitor commonly used in combination with an anti-CD20 mAb for the treatment of CLL. Unlike BTKi, the effects of venetoclax on immunity are less well understood. There is some evidence suggesting that successful treatment with venetoclax-based regimens may reduce the inherent immunosuppression seen in CLL patients [50]. During the height of the pandemic, the American Society of Hematology discouraged the use of venetoclax, unless it was considered the most appropriate treatment for a specific patient, as the initiation period requires multiple clinic visits. The recommendation also included considering the avoidance of anti-CD20 mAb [51].

In a national study conducted in Italy, involving 21 referral centers, 130 CLL patients initiated venetoclax +/− anti-CD20 mAb during the pandemic. All patients had relapsed CLL, with venetoclax being the preferred choice for half of them due to prior treatment with BTKi. While a quarter of the patients received single-agent venetoclax, others received combination therapy with anti-CD20 mAb. Venetoclax ramp-up and administration was not modified in any of the patients, and in only 17%, rituximab administration was postponed or had extended intervals. Among the patients, 16 (all unvaccinated) contracted COVID-19, with 75% experiencing severe disease, and 6 of them succumbing to the infection, 4 of whom had received rituximab [52].

In another Italian cohort, while only 67% of patients on BTKi had interrupted treatment, all patients on venetoclax-based regimen temporarily stopped the drug. Patients receiving any treatment had worse OS compared to untreated or previously treated patients [30]. Preliminary data from the German CLL13 trials reported seven cases of COVID-19, mostly occurring after discontinuing venetoclax-anti-CD20 mAb-based regimens. Among these cases, 6 required hospitalization, 2 required ICU admission, and 2 patients died. The observed rates were higher than those seen in the general population at the time, suggesting an ongoing immune dysfunction in these patients even during the post-therapy period [53].

SARS-CoV-2 Vaccines in Patients with CLL

The pivotal clinical trials evaluating efficacy and safety of the SARS-CoV-2 vaccines have reported effectiveness rates ranging from 67 to 95% in preventing SARS-CoV-2 infection (with mRNA vaccines demonstrating 94–95% efficacy) [54–57]. However, these trials excluded immunocompromised patients, including those with HM, necessitating the evaluation of vaccine efficacy and safety in this specific population. This is particularly important given that it has been well established that CLL patients have an impaired serological response to various vaccines, such as hepatitis B, zoster, pneumococcal, and others [58–62].

Since the initiation of the COVID-19 vaccination program, numerous studies have been published examining the response of HM and CLL patients to SARS-CoV-2 vaccines. Most of these studies have focused on assessing humoral responses and have consistently reported much lower seroconversion rates in CLL patients compared to healthy controls, ranging from 39% to 67%.

In a large prospective study involving 500 CLL patients, response rates to vaccination were 67% compared to 100% in healthy controls. Among responders, antibody titers were found to be 3.7 times lower than those in the control group [63]. Another large multicenter study conducted in Israel, which included 373 CLL patients, reported humoral response rates of 43% after two doses of the BNT162b2 mRNA vaccine [64]. Similarly, Herishanu et al. [65] reported a seroconversion rate of 39.5% in 167 CLL patients who received a similar vaccine regimen. A comparison of 52 CLL patients with 52 age- and sex-matched healthy controls revealed a significant reduction in response rate among CLL patients (52% vs. 100%, $p < 0.001$). Other large cohort studies have shown humoral response rates ranging from 52 to 64% [66, 67]. Several

recent meta-analyses have also described seroconversion rates in CLL patients ranging from of 40 to 67%, compared to 97–100% in healthy subjects [68–72].

CLL patients consistently exhibit lower antibody response compared to other HM in almost all studies. For instance, in a report by Herzog-Tzarfati et al. [73], CLL patients had the lowest antibody response rate at only 47%, while patients with CML, MDS, MPN, and HL had response rates ranging from 84 to 94%. Similarly, Šušol et al. [74] found a seroconversion rate of 39.6% in CLL patients after two doses of the BNT162b2 vaccine, compared to an overall seroconversion rate of 70.4% in HM.

Most studies have examined immunoassay-based humoral response to SARS-CoV-2 vaccines (mostly anti-Spike antibodies). Some studies have also assessed the neutralizing capabilities of antibodies in preventing the entry of the virus into host cells. These were used in subsets of patients and demonstrated correlation with anti-Spike antibody titers [75]. In CLL patients, Benjamini et al. [64, 76] showed a correlation between the presence and titer of anti-Spike-IgG antibodies and the level of neutralizing antibodies.

Risk Factors for Reduced Response

Various factors related to the disease and its treatment contribute to the diminished vaccine efficacy in CLL patients. Older age, low immunoglobulin levels, as well as any kind of active treatment, have consistently been associated with decreased immune response, including all commonly used targeted therapies, particularly current or recent anti-CD20 mAb.

Two large prospective studies conducted in Israel demonstrated lower seropositivity rates in older adults and those with low IgG level. Treatment naïve patients had significantly higher humoral response rates, ranging from 55 to 61%, compared to only 14–16% in patients on active therapy. Patients who were off-treatment exhibited higher response rates, ranging from 42 to 65%, and those in complete or partial remission had even higher responses than treatment naïve patients in one of the studies [65]. Patients who received anti-CD20 mAb within 12 months of vaccination had dismal response rates, ranging from 0 to 5%. Response rates were comparably low in patients receiving BTKi (16–18%) and venetoclax combinations (6–14%) [64, 65].

Parry et al. [63] also reported similar findings in CLL patients receiving mRNA or viral vector vaccines. They observed response rates of 78% in treatment-naïve patients, and interestingly, 62% in patients just prior to initiation of CLL-directed therapy. Response rates were lower in patients on therapy (43%), when anti-CD20 mAb was given within 12 months (24%) and under BTKi (30%). A recent meta-analysis of 27 prospective studies further confirmed these risk factors and response rates in CLL patients [72].

Response to Different Vaccine Types

Studies comparing response rates to different vaccines yielded inconsistent results. Some studies did not demonstrate a difference in humoral responses between mRNA vaccines and the adenoviral vector vaccine ChAdOx1 in CLL patients [63, 77]. Others reported higher clinical efficacy in cancer patients who were vaccinated with the BNT162b2 mRNA vaccine compared to ChAdOx1 (72% vs. 59%) [78].

Two prospective studies and one retrospective analysis showed higher humoral response rates with Moderna's mRNA-1273 vaccine compared to Pfizer's BNT162b2 in patients with HM or CLL specifically [66, 67, 79]. The difference in response between the two mRNA vaccines, despite their similar mechanism of action, could be attributed to factors such as the specific mRNA sequence, the lipid composition that may influence host cell penetration, or the amount of spike mRNA per dose, which is over three times larger in the mRNA-1273 vaccine [80]. Despite these studies, it is important to note that there is currently no robust evidence demonstrating a clear advantage of one mRNA vaccine over the other in CLL patients.

Seropositivity Persistence

Limited data are available regarding antibody persistence over time in CLL patients after COVID-19 vaccination. Studies by Tadmor et al. [81] and Herishanu et al. [82] demonstrated that the majority of patients who initially responded to the mRNA vaccine remained seropositive at 3–6 months (73–90%). However, antibody titers substantially decreased over time. The rate of antibody decay in CLL patients was comparable to that observed in healthy controls over 70 years old, but with much lower titers.

In a study by Shree et al. [83] which included 126 lymphoma patients, the persistence of immune response was evaluated when treatment was initiated after vaccination. Fifteen patients received the complete two-dose vaccine series before starting of anti-CD20 mAb treatment. Among these patients, ten achieved seroconversion, and the rates of antibody persistence during treatment were comparable to those of healthy controls.

Cellular Immunity

The role of cellular immunity in the response to anti-SARS-CoV-2 vaccines is currently less understood. Cellular immune responses are assessed using complex and costly techniques, which have not been commercialized and are not widely available. Studies evaluating cellular immunity have often focused on small subsets of patients using methods such as enzyme-linked immunosorbent spot (ELISpot) or intracellular cytokine staining to measure cytokine responses upon ex vivo stimulation with viral Spike-protein, or TCR sequencing to identify spike-specific T cells [84].

In a study involving 68 CLL patients who received two doses of BNT162b2 mRNA vaccine, T cell immune responses were observed in 32% of patients and were highly correlated with detection of anti-spike IgG antibodies. However, a quarter of seronegative patients did develop a cellular response [85]. In other studies, T-cell responses did not necessarily correlate with antibody titers or neutralizing antibodies [58, 76, 86–88]. Parry et al. [89] demonstrated similar cellular response rates in CLL patients compared to healthy controls after receiving two vaccine doses, despite the lower humoral response rates. Others reported that cellular immunogenicity showed better persistence over time than humoral responses [88]. Whether cellular responses, in the absence of seroconversion, confer sufficient clinical protection against SARS-CoV-2 infection, remains to be proven.

Strategies to Improve Vaccine Response

Studies that examined the response to subsequent booster doses of COVID-19 vaccines in CLL patients, who failed to respond to the initial vaccine series, have yielded varied results. Some studies have shown no response to booster doses in nonresponders [74, 90], while others have reported seroconversion rates ranging from 23 to 40% [66, 91, 92]. In patients who initially responded, booster doses have been shown to increase antibody titers [77]. For example, Benjamini et al. [76] reported a 10-fold increase in antibody titers in 67 CLL patients who received a fourth booster mRNA vaccine, but only 4 out of 34 patients who were seronegative prior to the injection seroconverted. Parry et al. [89] demonstrated an increase in response rate from 66% to 80% in a large cohort of CLL patients who received a third vaccine dose, with a 4.5-fold increase in antibody titers. However, there was no further increase in seroconversion rate after the fourth vaccine. Responses to booster doses were lower in patients on active treatment, particularly those with recent exposure to anti-CD20 mAb treatment [66, 76, 91].

Another strategy to improve response rates involves use of heterologous boosters, where different types of vaccines are administered for the booster dose. Studies in healthy adults have shown increased antibody titers with this approach [72, 93]. Few studies have reported on the efficacy of heterologous boosters in HM and CLL patients. One small uncontrolled study reported a 17% seroconversion rate after Ad26.COV2.S vaccine booster dose in 18 patients with CLL who showed no response to two doses of BNT162b2 vaccine [94]. In a large cohort of over 400 CLL patients, no difference in humoral response rates were observed with heterologous booster vaccination (mRNA booster after initial mRNA or ChAdOx1 vaccine), but cellular responses were significantly higher with the heterologous approach [89].

Vaccine Clinical Efficacy: Breakthrough Infection

Most studies in CLL have primarily focused on laboratory responses to vaccines. There is limited published data regarding the correlation between immune response and clinical efficacy of vaccines in CLL patients. In a retrospective cohort study, which was conducted prior to emergence of the Omicron variant, involving 984 vaccinated CLL patients (98% of whom received mRNA vaccines), the risk of breakthrough infection was found to be 15.2% among CLL patients, compared to 4.5% in the control group. Among all patients with hematological malignancies, the risk of hospitalization and mortality was significantly higher when compared to the healthy controls (37.8% vs. 2.2%; 5.7% vs. 0.8%, respectively) [95].

A population-based case-control study conducted in the UK, examined COVID-19 infections in a large cohort of 377,194 cancer patients during the spread of the delta variant (B.1.617.2). The study reported 42,882 breakthrough SARS-CoV-2 infections among vaccinated cancer patients. Among patients with lymphoma or leukemia, vaccine efficacy after the second dose was found to be low, ranging from 44% to 45%, compared to 69.8% in the control population. Furthermore, after 3–6 months from vaccination, efficacy in this population dropped to 13–19%, while remaining at 61% in the control group [78].

The EPICOVIDEHA survey documented episodes of breakthrough COVID-19 infection in a cohort of 1,548 vaccinated patients with HM (mainly mRNA vaccines), including 211 patients with CLL. In the entire cohort, the rate of severe infection was significantly lower than reported in the pre-vaccination era (41.7% vs. 63.8% pre-vaccination $p < 0.001$). The overall mortality rate was

9.2%, a marked improvement from the 31% mortality reported earlier in the pandemic by the same registry. However, clinical outcomes in CLL patients were still worse than those of the general population, with a mortality rate of 11.8%. The majority of infections in the cohort were caused by the Omicron variant (68.7%) [96]. Therefore, while there was an improvement in clinical outcomes, it is important to note that it may not be solely attributed to vaccine efficacy, but also to changes in viral variants and the introduction of effective mAbs and antiviral treatments.

An Italian prospective study investigated the humoral and clinical efficacy of SARS-CoV-2 mRNA vaccines in 364 patients with HM. Overall, 82% of patients were seropositive after two vaccine doses, with a seropositivity rate of 59% in the 22 patients with CLL. The incidence of breakthrough infections was 2.98 per 10,000 person-days, which increased to 9.82 after the spread of the Omicron variant. Seropositive patients had lower risk of infection, as well as reduced risk of severe infection and hospitalization. No correlation was found between cellular immunity, as evaluated by ELISpot, and vaccine efficacy, in a subset of patients (107 of 364) [97].

Vaccine Safety

As all vaccine approval trials excluded immunocompromised patients [54–57], safety of the vaccinations in this population needed to be addressed. Several large studies and a meta-analysis confirmed the safety of mRNA and vector-based SARS-CoV-2 vaccines in HM and CLL, reporting mostly mild adverse events with a safety profile similar to that observed in healthy adults [64, 65, 68, 98].

Other Strategies to Mitigate Risk of Severe Infection

In addition to standard prevention measures such as social distancing, hand washing, and face masks [99], there are currently several effective pharmacological options available that can help reduce the risk for progression to severe disease.

Pre-Exposure Prophylaxis with mAbs

Tixagevimab-Cilgavimab (Evusheld) is a monoclonal neutralizing antibody combination with an extended half-life that received emergency FDA approval on December 2021 for pre-exposure prophylaxis against SARS-CoV-2 in immunocompromised patients, based on the phase 3 PROVENT study that demonstrated a significant reduction in symptomatic SARS-CoV-2. However, this study included only a small percentage of patients with cancer (7%) and immunosuppressive therapy (3%) [100].

Benjamini et al. [101] conducted a study involving 50 CLL patients who received Tixagevimab-Cilgavimab. As expected, 98% showed a serological response. During a 3 months follow-up period, 26% acquired SARS-CoV-2, but none required hospitalization and all recovered without complications. In another large Israeli registry study, which included 703 immunocompromised patients (including 13% CLL patients), those who received Tixagevimab-Cilgavimab (150/150 mg) had a reduced rate of breakthrough infection during the Omicron surge compared to matched eligible patients who did not receive prophylaxis (10% vs. 13.4%, $p = 0.02$) The rates of hospitalizations were also reduced in the group that received the antibody treatment [102].

Another US registry study conducted during the Omicron surge reported an infection rate of 11% in 251 patients with B-cell malignancies who received a double dose of Tixagevimab-Cilgavimab (300/300 mg). However, among the 58 CLL patients included, rates were as high as 22%; the hospitalization rate was 15% in the entire cohort, and no deaths were reported [103].

Despite its initial benefit, the emergence of new circulating variants has rendered Tixagevimab-Cilgavimab ineffective and on January 2023 the FDA announced it is no longer authorized for emergency use in the USA [104]. Newer mAbs are expectedly awaited.

Post-Exposure Prophylaxis Strategies

Casirivimab-imdevimab (REGEN-COV) and Bamlanivimab-etesevimab are additional mAb combinations that target the SARS-CoV-2 spike protein. These antibodies demonstrated reduced mortality in high-risk patients with mild-moderate COVID-19 early in the pandemic [105–108] and showed to have potential benefit in hematological patients based on several case reports and small studies [37, 109, 110]. However, they are no longer in use as of early 2022, as they were shown to be ineffective against the Omicron variant [111].

Nirmatrelvir/ritonavir (Paxlovid) is an oral antiviral drug that has received emergency authorization in late 2021 in Europe and the USA. It is indicated for the treatment of symptomatic outpatients with mild-moderate SARS-CoV-2 infection who are at high risk for progression to severe disease. The approval was based on the EPIC-HR study, which reported a significant reduction in hospitalization or death by 88.9%, although

absolute risk reduction was small [112]. More recent data suggest that Nirmatrelvir/ritonavir is also effective against Omicron subvariants [113, 114].

In patients with HM, the EPICOVIDEHA SARS-CoV-2 infections registry demonstrated a significant reduction in mortality in 117 patients treated with Nirmatrelvir/ritonavir compared to 1,742 treated otherwise (2% vs. 11%, $p = 0.036$) [115]. Similarly, a retrospective registry study by Tadmor et al. [116], which included 1,080 CLL patients infected with SARS-CoV-2, reported a significant reduction in hospitalization or death in CLL patients over the age of 65, who received Nirmatrelvir/ritonavir (4.8% vs. 10.2%; relative risk reduction 69%). It is important to consider contraindications and potential drug-drug interactions, which are common in patients with CLL. Specifically, interaction exists with BTKi and venetoclax, and Nirmatrelvir/ritonavir can only be administered if those can be safely stopped for the duration of treatment [117].

Molnupiravir is another antiviral approved in the USA (but rejected by the European Medical Agency) for the same indication as Nirmatrelvir/ritonavir. Its approval was based on a phase 3 trial that demonstrated a reduced risk of the combined outcome of hospitalization or death (6.8% vs. 9.7%, $p = 0.001$) [118]. Although not compared directly in randomized trials, the benefit of Molnupiravir was not as robust as shown with Nirmatrelvir/ritonavir, and not all subsequent studies have consistently demonstrated efficacy [119]. Therefore, Molnupiravir can be considered as an alternative option when contraindications to Nirmatrelvir/ritonavir apply, such as advanced kidney or hepatic impairment, or significant drug-drug interactions.

In a cohort of 175 hematological patients treated with Molnupiravir, of whom 77% were vaccinated, the rates of hospitalization and death at 28 days were 20% and 4% respectively. These outcomes were better than those previously reported in vaccinated hematological patients [120]. A matched-paired analysis from the EPICOVIDEHA registry, comparing the use of Molnupiravir versus Nirmatrelvir/ritonavir in 232 patients with HM (including only 9 with CLL), reported similar rates of SARS-CoV-2 severity, hospitalization or mortality between the two drugs [121].

Remdesivir, a parenteral antiviral agent, has been shown to shorten recovery time from SARS-CoV-2 infection and reduce the risk of hospitalization in unvaccinated outpatient populations, although no mortality benefit has been demonstrated due to lack of events [122]. A retrospective study, conducted during the early stages of the pandemic, demonstrated a survival benefit in CLL patients [27]. In a recent study that included only 4.2% cancer patients, a new oral formulation of remdesivir demonstrated noninferiority to Nirmatrelvir/ritonavir with regard to time to clinical recovery [123].

High-titer convalescent plasma (CCP) remains an option for use in selected high-risk patients, although there are conflicting results among different studies [124–126]. The heterogenicity of results is likely related to differences in inclusion criteria, the stage of disease in which CCP was administered, plasma antibody titer, and changes in circulating variants. A systematic review of over 2,000 hospitalized immunocompromised patients suggested a mortality benefit [127]. Another systematic review focusing on patients with HM, reported improved clinical outcomes without associated adverse events. This review included data from 258 patients included in four observational and retrospective studies and thirteen case reports [128]. A randomized controlled trial, involving 120 hospitalized patients with mild-moderate COVID-19 disease, including 49 immunocompromised patients, did not show benefit in the entire cohort but reported a significant reduction in mortality among the subset of immunocompromised patients (HR 0.37) [129]. Additionally, a cohort study of 112 patients with HM (12% with CLL) and COVID-19 infection, reported a survival benefit in patients with B-cell neoplasms who were treated with CCP [130].

Expert Recommendations

The recommendations on patient management during COVID-19 pandemic have rapidly evolved over time, and even the latest guidelines may now be out of date. These recommendations mostly regard patients with HM in general, with some comments on CLL specifically.

WHO and the CDC strongly recommend the use of masks in higher risk situations, including for individuals at high risk of severe complications from COVID-19, which inevitably includes patients with CLL [99, 131]. However, local practices may vary widely and are dictated by national or institutional regulations. The International COVID-19 Blood Cancer Coalition (ICBCC) acknowledges the growing public fatigue with health measures and thus emphasizes the importance of prophylactic measures and therapeutic interventions in patients who contract COVID-19 infection [132].

COVID-19 vaccination is recommended for all patients with CLL and their household members [133]. Ideally, vaccination should be completed before commencing therapy. However, routine testing for COVID-19 antibodies is currently not recommended. Booster

doses are recommended, as data shows at least some improvement in seroconversion rates and antibody titers. Most guidelines currently recommend administering a third and even fourth primary dose to all CLL patients. There are no specific recommendations regarding the type of vaccine to be used. Pre- and post-exposure prophylactic mAb are no longer endorsed, due to their ineffectiveness during the Omicron era, as discussed earlier [134]. Measures for the rapid detection and management of COVID-19 infection for high-risk individuals should be implemented. Since patients with HM, and with CLL specifically, are at a particular risk for severe disease and death, symptomatic patients should be encouraged to test as soon as possible. In case of a COVID-19 diagnosis, patients should receive post-exposure antiviral therapy within 5 days of disease onset, according to disease severity and local drug availability [132].

The treatment approach for CLL should follow consensus guidelines. "Watch and wait" strategy is recommended for asymptomatic patients with low tumor burden. When treatment is indicated, it is the premise of most guidelines that patients should receive the best treatment option considering disease and patient-specific factors. In the midst of the pandemic, some recommended prioritizing treatments that could be administered in the outpatient setting, requiring fewer clinic visits and laboratory assessments. Avoidance of anti-CD20 mAb was also suggested. However, as the pandemic abated or was under control per local authorities, and as treatments that mitigate risk of disease complications became available, physicians were encouraged to follow standard guidelines for CLL treatment and not consider COVID-19 as a primary factor in decision making [51, 135].

Conclusion

Patients with CLL constitute a unique population with significant immunodeficiency and a high risk for severe COVID-19 disease, leading to substantial rates of complications and mortality. These patients exhibit diminished humoral and cellular responses to anti SARS-CoV-2 vaccines, particularly with ongoing or recent therapy. Therefore, while CLL-directed therapy should be guided by disease and patient specific factors, management of CLL patients requires continuous vigilance, alertness, and prompt response in case of COVID-19 infection.

Conflict of Interest Statement

R.H. has no conflicts of interest to declare. G.I. has accepted honoraria from AbbVie, Janssen, and AstraZeneca, Sanofi, and research grants from AbbVie, Janssen, and AstraZeneca.

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