How We Manage Patients With Chronic Lymphocytic Leukemia During the SARS-CoV-2 Pandemic

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Abstract

Infections are a major cause of morbidity and mortality in patients with chronic lymphocytic leukemia (CLL). These can be exacerbated by anti-leukemic treatments. In addition, the typical patients with CLL already have fragilities and background risk factors that apply to the general population for severe COVID-19. On these bases, patients with CLL may experience COVID-19 morbidity and mortality. Recurrent seasonal epidemics of SARS-CoV-2 are expected, and doctors taking care of patients with CLL must be prepared for the possibility of substantial resurgences of infection and adapt their approach to CLL management accordingly. In this Guideline Article, we aim at providing clinicians with a literature-informed expert opinion on the management of patients with CLL during SARS-CoV-2 epidemic.

Introduction

Many countries are following SARS-CoV-2 non-pharmaceutical mitigation policies, and, with the current data, it is impossible to determine how long such policies will be needed to establish sufficient herd immunity. Modeling suggests recurrent SARS-CoV-2 epidemic phases flaring up on the background of an endemic disease dictated by relaxation and reinstitution of the package of non-pharmaceutical interventions until an effective pharmacological treatment/prevention against COVID-19 will be available.[1,2]

The rapidly expanding SARS-CoV-2 pandemic and its threats require a quick reaction prior to the availability of (eagerly awaited) evidence on how to manage patients with chronic lymphocytic leukemia (CLL) during this pandemic. Accordingly, this document was prepared by adapting existing guidance and

scientific evidence to the new scenario imposed by the SARS-CoV-2 epidemics.

The aim of this document is to provide clinicians with a literature-informed expert opinion (Table 1) developed through a bottom-up information processing and based on incoming data from publications and the clinics in SARS-CoV-2 infection and related infectious conditions including other oncological diseases.

Search strategy and selection criteria

A literature review was performed using PubMed to identify relevant English-language articles published through April 30, 2020 [search terms (coronavirus OR COVID OR SARS-CoV OR *nCoV*) AND (immunodeficiency OR leukemia OR cancer)]. Recommendations on the general themes of SARS-CoV-2, COVID-19 and CLL or cancer provided by ASH, ASCO, ASTCT,

Table 1

Summary of Recommendations About Management of Patients With CLL During the COVID-19 Pandemic.

General considerations	• We consider patients with CLL at increased risk of SARS-CoV-2 infection and COVID-19 morbidity and mortality due to their immune defect and fragility similar to patients with other malignancies.
	• We limit patients' exposure to potential nosocomial SARS-CoV-2 infection by minimizing the number of visits, postponing in-hospital routine follow-up appointments, and substituting them with remote check-ins.
	• Routine lab samples are often omitted in the absence of new or increasing symptoms and, in case they are needed, local/home collection is a viable option.
Management of patients with CLL needing therapy during the pandemic	• For patients in need of treatment, we recommend postponing initiation of therapy, if possible, until the epidemic trajectory is decreasing.
	• When treatment cannot be further deferred, we use the systemic therapy that requires fewer clinic visits and/or is less immune suppressive.
Management of patients with CLL undergoing anti-leukemic therapy during the pandemic	• We test asymptomatic patients for SARS-CoV-2 infection by nasopharyngeal swab RT-PCR 72-24 hours before starting CLL therapy.
	• During treatment, patients are questioned for clinical manifestations consistent with COVID-19, including atypical symptoms, over the phone or at the clinic's door.
Management of patients on treatment for CLL lacking evidence of COVID-19	• We continue treatment with targeted agents in patients lacking COVID-19 symptoms as in normal circumstance with exception of anti-CD20 antibodies.
	• In patients already receiving prophylactic immunoglobulin replacement therapy, the infusions will be used less frequently or replaced with s.c. formulations if available and patients can self-administer them at home.
	• We encourage to maintain the vaccination program in place at the treating institution including, in particular, against seasonal influenza and Streptococcus pneumoniae if not previously done.
Management of patients on treatment for CLL who receive a COVID-19 diagnosis	• In patients on treatment for CLL, who receive a COVID-19 diagnosis, holding therapy until the recovery from infection is a prudent approach.
	• We resume targeted agents if all the following conditions are met:
	i) the patient is asymptomatic for at least 48 hours;
	ii) at least 14 days have elapsed from symptoms start;
	iii) at least two consecutive RT-PCR tests are negative on nasopharyngeal swab samples collected each approximately one week apart.

CDC, EBMT, EHA, ERIC, ESMO, iwCLL, NCCN, NIH, SSC, and WHO were also reviewed (last search on April 30th, 2020).

General considerations

We consider patients with CLL at increased risk of SARS-CoV-2 infection and COVID-19 morbidity and mortality due to their immune defect and fragility similar to patients with other malignancies

Whether the prevalence of COVID-19 in patients with cancer, including CLL, is higher than in sex- and age-matched normal population is uncertain.[3–5] However, there is evidence that cancer conveys a poorer outcome in patients with COVID-19 infection.[3–10] In addition, the risk of COVID-19 morbidity and mortality is thought to be higher in CLL due to the detrimental effect of comorbidities frequently occurring in patients with this leukemia, though this aspect has not been specifically addressed.

CLL can result in one or more of the following risk factors for infection: hypogammaglobulinemia, qualitative and quantitative B and T cell defects including impaired response to vaccination and CD4+ lymphopenia, innate immune dysfunction, and neutropenia among others.[11] These can be exacerbated by anti-leukemic treatments and are known risk factors for viral infections.[12,13] Thus, we can speculate that this existing immune suppression might also prevent or delay CLL patient's ability to react against the SARS-CoV-2 virus or to cope with COVID-19.

In addition, the typical patient with CLL may already have background risk factors for life-threatening COVID-19 that apply to the general population. Notably male gender, age >65 years, and medical conditions such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension, other cancers, chronic kidney disease, and >2 underlying diseases are known risk factors of morbidity and mortality from COVID-19.[14–16] Accordingly, around 70% of patients with CLL are male, 70% are older than 65 years, 25% harbor >2 comorbidities, 21% have hypertension, 13% cardiovascular disease, 26% diabetes, and 5% chronic respiratory disease.[17,18]

Communication with patients can both mitigate emotional outcomes and improve adherence to public health, non-pharmaceutical interventions aiming at reducing the risk of infection.[19]

We limit patients' exposure to potential nosocomial SARS-CoV-2 infection by minimizing the number of visits, postponing in-hospital routine follow-up appointments, and substituting them with remote check-ins. Routine lab samples are often omitted in the absence of new or increasing symptoms and, in case they are needed, local/home collection is a viable option

There is solid evidence supporting that, in the absence of a vaccine, the sole effective prevention of SARS-CoV-2 infection and COVID-19 is public health, non-pharmaceutical interventions aimed at reducing contact rates in the population and thereby reducing transmission of the virus.[20–28] Nosocomial spread of SARS-CoV-2 across patients and health-care professionals is a serious concern.[29–32] The final goal should be to have COVID-19 free environments for safely and routinely taking care of patients with CLL, also during both endemic and future epidemic outbreaks, particularly in institutions with dedicated cancer centers.[33]

Access to the hospital for investigations that are not iwCLL guideline recommended must be avoided to prevent nosocomial

SARS-CoV-2 infection. Marrow aspirate and biopsy generally are not required for the diagnosis of CLL.[34] The staging of CLL does not use CT scans but relies on physical examination and blood counts.[34] The majority of relapses or progressions in CLL are detected by physical examination and blood counts, not by imaging studies.[35] For patients enrolled in clinical trials, the patient's safety remains a priority and it is better to avoid all unnecessary visits, CT scans and lab tests requested per protocol, following regulatory agencies and/or sponsor ad hoc guidelines. Only those exams that will have a direct impact on the clinical management of patients should be performed and in-hospital visits should be replaced with remote consultations.

Management of patients with CLL needing therapy during the pandemic

For patients in need of treatment, we recommend postponing initiation of therapy, if possible, until the epidemic trajectory is decreasing

CLL is a chronic disease that very rarely poses an imminent risk of death even when it is in advanced stage. The risk of death from COVID-19 in patients with CLL has not yet been established, making it difficult to balance the risks of SARS-CoV-2 infection and those of starting, deferring, or halting treatment on life expectancy. Nevertheless, under an epidemic scenario, we estimate the risks of community and nosocomial infection by SARS-CoV-2 and of complicated COVID-19 higher than the risk of delaying CLL treatment. Under an endemic scenario (ie, Rτ <1, where Rτ is the average number of secondary infections produced when one infected individual is introduced into a host population where everyone is susceptible, Rτ >1 indicates that outbreak will lead to an epidemic, and Rτ <1 that the outbreak will become extinct),[36] we estimate the benefit of a treatment known to prolong the survival of patients with CLL higher than the risks of community and nosocomial infection by SARS-CoV-2 and symptomatic COVID-19.

This reasoning is based on the following indirect evidence. First, in cancer patients, the COVID-19 case fatality rate is estimated to be 6% to 7%.[6–8,10,37,38] Unadjusted statistics point to a higher mortality by COVID-19 among cancer patients than in the general population.[4,5] Likewise, in a retrospective study during the 2009 influenza A (H1N1) virus pandemic, cancer patients had a higher incidence of 30-day mortality (18%) compared with the general population.[39] Second, a pattern of decreasing risk of death was reported for the Middle East respiratory syndrome as the infection reproduction number declined toward a more endemic level (Rτ <1).[40] Third, the introduction of chemo(immuno)therapy and targeted agents in the treatment of CLL led to a 6% relative survival improvement and to a 10% decrease of deaths per 100-patient/year compared to palliative therapies used in the 1980s.[41,42]

The decision about delivering treatment should be primarily influenced by the tempo of SARS-CoV-2 epidemiology, the local situation of the hospital and the potential therapeutic benefit of the anti-leukemic therapy. CLL rarely conveys the need for immediate, urgent therapy that cannot be postponed a few weeks while waiting for a decline of the outbreak and a safer delivery of the drugs. Therefore, during the rise and the peak of the SARS-CoV-2 epidemic, we strongly consider the possibility of delaying the start of a treatment even in advanced stage CLL. It is known that advanced stage CLL is seldom complicated by life-threatening end organ damage or profound, debilitating symptoms requiring

immediate treatment. In addition, it is important to note that lymph node size and degree of cytopenia do not affect progression free survival of targeted treatment of CLL,[43–61] and that cytopenias may remain stable over an extended period slightly below the suggested thresholds to initiate therapy.

Bulky disease, as per iwCLL guidelines, is defined as >10 cm lymph node size but this should not be axiomatically assumed to be synonymous with impending organ compression[34] and should be carefully evaluated on an individualized basis. In both treatment naïve and relapsed CLL, bulky lymphadenopathy occurs in only 10% of patients.[43–61]

The iwCLL recommends starting therapy when the Hb level is <10 g/dL, as a proxy of lower quality of life and cardiovascular risk; in other conditions, symptomatic anemia rather than a defined cut-off is used to trigger intervention. Iron deficiency with or without anemia is a frequent complication in lymphoid malignancies and more in general in cancer, occurring in approximately 40% of cases and must be considered in the differential diagnosis of anemia.[62,63]

Decreased hemoglobin for autoimmune hemolytic anemia can be managed with a course of corticosteroids and it is not an indication for anti-CLL treatment. Corticosteroids have the largest evidence of activity in CLL-related autoimmune hemolytic anemia and are the guidelines-recommended first line treatment.[34] It is not known whether corticosteroids increases the risk of SARS-CoV-2 infection or mitigates its severity.[29,64–70] Clinical trials with novel agents excluded patients with uncontrolled autoimmune hemolytic anemia.[43–46,54,56,58,59] However, treatment with BTK inhibitors facilitate withdrawal of ongoing immune suppressive agents in controlling hemolytic manifestations.[71]

For platelets, according to the 2018 update of the iwCLL guidelines, a count <100 × 10^9/l does not require immediate therapeutic intervention and can be tolerated, according to the bleeding risk, with regular monitoring.[34] One should also remember that thrombocytopenia may be a feature of the initial presentation of COVID-19.[72–74] Immune thrombocytopenia can be effectively treated with corticosteroids but also with agents that are not immunosuppressive, such as intravenous immunoglobulin and oral thrombopoietic (TPO) agents.[75] Up to 78% of patients with CLL and immune thrombocytopenia respond to eltrombopag.[76] Potential increased risk of thrombosis, which is also a concern in COVID-19,[77] has been reported with the use of TPO agents and should be taken into account.[75] While prophylactic anticoagulation is recommended for hospitalized COVID-19 patients, its use in the outpatient setting for COVID-19 thrombosis prevention is not supported by prospective clinical trial data.

Disease-related symptoms (ie, extreme fatigue; unintentional weight loss ≥10% within the previous 6 months; fever > 38.0°C for 2 or more weeks without evidence of infection; drenching night sweats for ≥1 month without evidence of infection) or short lymphocyte doubling time (LDT) are very infrequently (~5%) the only reason to start therapy and we emphasize carefully excluding causes other than CLL.[34,78] Prolonged observation can sometimes show improvement of systemic symptoms or LDT.

When treatment cannot be further deferred, we use the systemic therapy that requires fewer clinic visits and/or is less immune suppressive

The rationale of the recommendation is to reduce the risk of nosocomial SARS-CoV-2 infection by reducing hospital visits and to avoid chemo(immuno)therapy, idelalisib plus rituximab

and duvelisib, due to the concern about a higher risk of infection. Based on these considerations, we suggest ibrutinib or acalabrutinib and, for logistical reasons, venetoclax for patients not fitting for BTK inhibitors. We use BTK inhibitors as mono-therapies instead of rituximab or obinutuzumab combinations and delay combining anti-CD20 monoclonal antibodies with venetoclax until later in the course of treatment when safer.

Ibrutinib, acalabrutinib, and venetoclax prolong progression-free and overall survival with lower risk of infections and similar/lower need for hospital care when compared to chemo(immuno) therapy.[43–46,54,56,58,59] The percentage of opportunistic infections reported for ibrutinib is low (4.1%) and similar to that reported for venetoclax (3.1%).[79–82] Compared to chemo (immuno)therapy, ibrutinib and acalabrutinib do not produce lymphopenia, a known risk factor for severe COVID-19.[79,83–85] The incidence of any ≥3 grade adverse events does not differ between ibrutinib (41%–77%), acalabrutinib (50%), and venetoclax (78%), indicating that the frequency of unplanned visits for adverse event management is likely to be similar for the 3 drugs.[43–45,54,56,58] Venetoclax may require additional unplanned visits for tumor lysis management during the ramp up phase.

Ibrutinib treatment requires few routine treatment visits and lab assessments.[54] It is associated with a low risk of neutropenia, and the immune reconstitution of T-cells, which in turns decreases the infection rate after the first 6 months of therapy.[54,80,84,85] BTK inhibitors are also undergoing investigation (NCT04346199) as an anti-inflammatory therapy in COVID-19, based on a few reports from uncontrolled clinical cases.[86,87] The disadvantage of ibrutinib treatment during SARS-CoV-2 outbreak is the continuous schedule not allowing treatment free intervals. However, if ibrutinib is discontinued because of an adverse event while CLL is in remission, the disease may continue being under control for a prolonged period of time before an alternative therapy is required.[46,50,88–90]

Venetoclax monotherapy preserves T-cells, and immuno-globulins, while transiently reducing the B-lymphocyte count. B-lymphocytes recover to normal levels within an average of 60 days from venetoclax discontinuation.[83,91] The disadvantage of venetoclax treatment is the need for frequent access to the hospital during the ramp-up phase to prevent tumor lysis syndrome (TLS).[58] In addition, venetoclax treatment has a relatively high risk of neutropenia during the first 3 months, though it does not translate into a high rate of infections and can be easily prevented through the use of G-CSF.[79] There is no evidence to support if, and to what extent, neutropenia is predictive of a negative outcome in SARS-CoV-2 infection.

Idelalisib and other approved PI3K inhibitors cause hyper-activation of the immune system resulting in significant autoimmune adverse events, including pneumonitis, and increase the risk of opportunistic infections, particularly when given as front-line therapy or in combination with anti-CD20 monoclonal antibodies.[92,93] In addition, in the relapsed setting, idelalisib plus rituximab treated patients have a shorter progression free survival and a higher drug discontinuation rate due to adverse events compared to acalabrutinib treated patients.[59]

Treatment with rituximab or obinutuzumab produces a marked decrease of B-lymphocytes that may persist for a long time after treatment discontinuation.[94] Rituximab therapy may facilitate JC and hepatitis B viral reactivation.[95,96] Humoral immunity appears to facilitate COVID-19 recovery.[97]

Management of patients with CLL undergoing anti-leukemic therapy during the pandemic

We test asymptomatic patients for SARS-CoV-2 infection by nasopharyngeal swab RT-PCR 72-24 hours before starting CLL therapy. During treatment, patients are questioned for clinical manifestations consistent with COVID-19, including atypical symptoms, over the phone or at the clinic's door

RT-PCR is the standard diagnostic test though its performance on nasopharyngeal swab for SARS-CoV-2 shows variable sensitivities ranging from 40% to 70%, but are consistently higher than RT-PCR of oropharyngeal swab.[98–102] False negative RT-PCR tests have been reported in patients with CT findings of COVID-19 who were eventually tested positive on lower respiratory tract specimens or with serial upper respiratory tract samplings.[103]

We monitor closely symptoms and keep a high suspicion for COVID-19 during treatment. Typical symptoms of COVID-19 are fever, myalgia, chills, coryza, cough, shortness of breath or sore throat. Gastrointestinal symptoms, as diarrhea, nausea, anosmia and ageusia can precede the development of fever and lower respiratory tract symptoms.[104–106] The specificity of such symptoms toward COVID-19 diagnosis is decreased because they may overlap with common adverse events of CLL therapies. In addition, sensitivity of infection-control strategies only based on symptoms triage is limited and these policies are not sufficient to prevent transmission of SARS-CoV-2, with up 50% of SARS-CoV-2 infections detected in an asymptomatic or pre-symptomatic condition in a skilled nursing facility.[107,108]

In patients developing symptoms consistent with COVID-19, we immediately isolate the patient and proceed to a comprehensive evaluation (SARS-CoV-2 RT-PCR on nasopharyngeal swabs, chest imaging studies, multiplex-nucleic antigen test including influenza, and other respiratory viruses and pathogens like pneumococci). We might offer imaging of the chest in patients without SARS-CoV-2 detected in the upper respiratory tract by RT-PCR but with clinical symptoms of lower respiratory infection.

Patients with CLL may have infectious diseases other than COVID-19, while COVID-19 symptoms are similar to other respiratory infections. Differential diagnoses must therefore include influenza and respiratory tract diseases. Indeed, even during the epidemic up to 50% of patients with fever and respiratory symptoms from the general population are positive for respiratory pathogens other than SARS-CoV-2, depending on the seasonal outbreaks and geographic location.[9,109–111] In addition, approximately 10% to 50% of patients with COVID-19 have superinfections.[9,111–113]

Management of patients on treatment for CLL lacking evidence of COVID-19

We continue treatment with targeted agents in patients lacking COVID-19 symptoms as in normal circumstance with exception of anti-CD20 antibodies

We do not apply prophylactic interruption or dose reductions of ibrutinib, acalabrutinib or venetoclax based on the reasoning that once treatment has started, the dose intensity should be preserved

to grant the maximum benefit. This is illustrated by the evidence that temporary ibrutinib dose interruptions associate with shorter progression free survival, suggesting that patients who are able to better adhere to treatment may derive more benefit.[46,58,90,114–119]

In patients already receiving prophylactic immunoglobulin replacement therapy, the infusions will be used less frequently or replaced with s.c. formulations if available and patients can self-administer them at home

Physicians need to be aware that immunoglobulins are not specifically effective against SARS-CoV-2 because of a lack of specific antibodies within the product, but can help in preventing additional infections. Bacterial secondary infection can complicate viral infections, a situation well known in influenza, and emerging in COVID-19.[120,121] Immunoglobulin replacement therapy reduces the risk of major infection in patients with CLL and low serum IgG.[122] Subcutaneous formulations are non-inferior to intravenous formulations with the advantage of being self-administered by patients at home after a short training.[123] Given the higher risk of thromboembolic events with COVID-19, we recommend assessment of risks vs. benefits in each patient and close monitoring for thromboembolic symptoms.

We encourage to maintain the vaccination program in place at the treating institution including, in particular, against seasonal influenza and Streptococcus pneumoniae if not previously done

Due to the known susceptibility of patients with CLL to common infections, it is wise to protect them through vaccination including the common seasonal diseases such as influenza to limit diagnostic confusion in case of symptoms.[121] In some institutions, anti-meningococcal vaccination is also included.

Management of patients on treatment for CLL who receive a COVID-19 diagnosis

In patients on treatment for CLL, who receive a COVID-19 diagnosis, holding therapy until the recovery from infection is a prudent approach

Patients with CLL may be already at increased risk of developing life threatening COVID-19 for multiple reasons, including the underlying cancer, disease-related immune suppression, age, concomitant medical conditions and the immune suppressive effect of most CLL therapies.[117–119,124] Thus, if the patient is receiving CLL therapy, its continuation should be carefully considered against the risk of drug-related immune suppression even in cases with mild COVID-19 symptoms. Occasional patients on BTK inhibitors, particularly those recently started and in whom the disease is not yet well controlled, may develop tumor flare with drug hold, which usually resolves rapidly with resumption of the inhibitor. However, most patients with well-controlled disease will remain stable during drug hold.

Despite mild symptoms at the onset of COVID-19, clinicians should be aware that patients at risk of life threatening COVID-19 could sometimes rapidly deteriorate, 1 to 2 weeks after illness onset.[117–119,124] We counsel the COVID-19 team to closely monitor these patients with remote 24/24 hours home health care and real time rapid evaluation of complications or with hospitalization. Remdesivir is the sole approved pharmaceutical agent effective at treating severe COVID-19. Use of investigational therapies for treatment of patients with CLL and with COVID-19 should ideally be done in the context of randomized controlled trials.[117–119,124]

We resume targeted agents if all the following conditions are met: (i) the patient is asymptomatic for at least 48 hours; (ii) at least 14 days have elapsed from symptoms start; (iii) at least two consecutive RT-PCR tests are negative on nasopharyngeal swab samples collected each approximately one week apart.

Beyond day 10 after symptom onset there is little residual risk of infectivity, based on cell culture of upper respiratory tract specimens, despite residual viral RNA shedding detected by RT-PCR.[100] The median range of SARS-CoV-2 viral shedding among patients with COVID-19 may indeed be up to 20 days from symptoms and may persist over longer periods in older persons, in those who received immunosuppressive therapy, and in those who had severe illness requiring hospitalization.[98–102,125–130]

One single RT-PCR test on nasopharyngeal swab has up to 15% false negative results when performed at the time of COVID-19 recovery. It is likely that 2 negative RT-PCR tests on nasopharyngeal swab samples collected 24 hours apart may not be sufficient for viral clearance evaluation, since an average of 7 ± 3 days between two tests is required to exclude an initial false negative assessment.

Appearance of specific IgG might also be informative, keeping in mind that the immunosuppression of patients with CLL in particular under anti-leukemic treatments may hamper a robust response. Seroconversion coincides with a slow but steady decline of sputum viral load and clinical recovery from COVID-19.

We would be prudent in resuming chemoimmunotherapy and consider a longer delay.

Conclusion

If SARS-CoV-2 will transit from an epidemic to an endemic state, recurrent seasonal epidemics of SARS-CoV-2 are expected, and if immunity to SARS-CoV-2 wanes in the same manner as in related coronaviruses, recurrent wintertime outbreaks are likely to occur. The total incidence of SARS-CoV-2 through 2025 will depend crucially on the proportion of patients developing efficient immunity and its duration, as well as the availability of a vaccine and effective therapy. Doctors taking care of patients with CLL must be prepared for possible outbreaks of the infection and adapt the management of patients with CLL accordingly, by reintroducing strict preventive measures during SARS-CoV-2 reappearance, while relaxing them during the post-epidemic period until virus extinction. An expert opinion is the sole evidence that can be provided at the moment, given the lack of any specific data about COVID-19 in CLL. As understanding of SARS-CoV-2 and COVID-19 and the available information evolves, we expect the proposed approach will be modified in the future.

We hope that the comments and recommendations made in this paper are useful to the global medical community, patients with CLL and physicians looking after them. Also, that they serve as background for further refinement as our understanding of SARS-CoV-2 and

COVID-19 infection unfolds, a process which requires a continued multidisciplinary and international collaboration.

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