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,
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 frailty 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. However, there is evidence that cancer conveys a poorer outcome in patients with COVID-19. 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. These can be exacerbated by anti-leukemic treatments and are known risk factors for viral infections. 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. 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.

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

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. Nosocomial spread of SARS-CoV-2 across patients and health-care professionals is a serious concern. 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.

Access to the hospital for investigations that are not iwCLL guideline recommended must be avoided to prevent nosocomial infections.
SARS-CoV-2 infection. Marrow aspirate and biopsy generally are not required for the diagnosis of CLL.4,14 The staging of CLL does not use CT scans but relies on physical examination and blood counts.4,15 The majority of relapses or progressions in CLL are detected by physical examination and blood counts, not by imaging studies.15 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.6

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, Rt < 1), where Rt is the average number of secondary infections produced when one infected individual is introduced into a host population where everyone is susceptible, Rt > 1 indicates that outbreak will lead to an epidemic, and Rt < 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%.8,9,10,13,38 Unadjusted statistics point to a higher mortality by COVID-19 among cancer patients than in the general population.8,9 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 patients with 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,43,47 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 and should be carefully evaluated on an individualized basis. In both treatment naïve and relapsed CLL, bulky lymphadenopathy occurs in only 10% of patients.48,49

The iwCLL recommends starting therapy when the Hb level is <10g/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.50,51

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.14 It is not known whether corticosteroids increases the risk of SARS-CoV-2 infection or mitigates its severity.29,64–66 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 x 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
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.\textsuperscript{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.\textsuperscript{103}

We monitor closely symptoms and keep a high suspicion for COVID-19 during treatment. Typical symptoms of COVID-19 are fever, myalgia, chills, corzya, 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{9,109-111} In addition, approximately 10% to 50% of patients with COVID-19 have superinfections.\textsuperscript{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.\textsuperscript{119,124–126} 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.\textsuperscript{117–119,124}

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 common infections. Bacterial secondary infection can complicate viral infections, a situation well known in influenza, and emerging in COVID-19.\textsuperscript{120,121} Immunoglobulin replacement therapy reduces the risk of major infection in patients with CLL and low serum IgG.\textsuperscript{122} Subcutaneous formulations are non-inferior to intravenous formulations with the advantage of being self-administered by patients at home after a short training.\textsuperscript{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 thrombembolic 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{117–119,124} We counsel the COVID-19 team to closely monitor these patients with remote 24/24 hours home health care 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.

Sources of Funding

DR received honoraria from Abbvie, AstraZeneca, Gilead, Janssen, Roche, Verastem, and research funding from Abbvie, Gilead, Janssen, CelsISTA; MS received honoraria from Abbvie, Genentech, Astra Zeneca, Sound Biologics, Pharmacyclics, Verastem, ADC Therapeutics, Celector, Bristol Myers Squibb and Atara Biotherapeutics, and research funding from Mustang Bio, Celgene, Bristol Myers Squibb, Pharmacyclics, Gilead, Genentech, Abbvie, TG Therapeutics, Beigene, Astra Zeneca, Sunesis, Acerta Pharma, Beigene and Merck; JRB received honoraria from AbbVie, Acerta, AstraZeneca, BeiGene, Catapult Therapeutics, Dynamo Therapeutics, Genentech/Roche, Gilead, Juno/Celgene, Kite, Loxo, Novartis, Pfizer, Pharmacyclics, Sunesis, TG Therapeutics Janssen, Teva and Verastem, received research funding from Gilead, Loxo, Sun and Verastem, and is a member of the data safety monitoring board for Morphosys and Invectys; JCB received honoraria from Astra Zeneca, Acerta, Janssen Oncology, Pharmacyclics, and Verastem and research funding from Acerta, Pharmacyclics, and Celgene; GG received honoraria from Abbvie, Janssen, Roche, Teva and Verastem, and is a member of the data safety monitoring board for Morphosys and Invectys; JCB received honoraria from Astra Zeneca, Acerta, Janssen Oncology, Pharmacyclics, and Verastem and research funding from Acerta, Pharmacyclics, and Celgene; GG received honoraria from Abbvie, Janssen, AstraZeneca, Sunesis. MM received honoraria from Roche, Gilead, Mundipharma, Janssen, Celgene, Pharmacyclics, Abbvie and research funding from Roche, Gilead, Mundipharma, Janssen, Celgene, Pharmacyclics, Abbvie; PH received honoraria from Acerta, Janssen, AbbVie; Pharmacyclics, Gilead and Roche; AM received honoraria from TG Therapeutics, Abbvie, Pharmacyclics, Johnson & Johnson, Regeneron, Astra Zeneca, Genentech, LOXO, and Celgene, and research funding from TG Therapeutics, Abbvie, Pharmacyclics, Johnson & Johnson, Regeneron, Genentech, LOXO, PORnola, DTRM, and Acerta; PG received honoraria from AbbVie, Acerta/ AstraZeneca, Adaptive, ArQuile, BeGene, CelGene/Juno, Dynamo, Gilead, Janssen, Sunesis, and research funding from AbbVie, Gilead, Janssen, Novartis, Sunesis.

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