infection has been detected in 55% (6/11) of cases: two had contacts with COVID-19 positive subjects, and four had occupational exposure (three are nurses working in hospital or assisted living facilities).

Three patients were asymptomatic. One patient (#3 in supplementary information) was admitted for high fever and bone marrow hypoplasia, lymphopenia, and agranulocytosis (on treatment with deferiprone) and tested positive at the third swab. Six out of 11 were hospitalized, but no one required mechanical ventilation. The patient with more severe symptoms who required more intensive ventilation support with continuous positive airway pressure (CPAP) has a history of diffuse large B-cell lymphoma, treated with chemotherapy in the previous year, currently in complete remission. Of the six people admitted to the hospital, only three received supposedly specific treatment for COVID-19: one hydroxychloroquine (HCQ), one HCQ plus ritonavir/darunavir, and one HCQ plus anakinra. Patient #3 did not receive HCQ due to concomitant therapy with amiodarone and an increased risk of *life-threatening* arrhythmia. The clinical course ranged from 10 to 29 days. Ten patients have clinically recovered and are on a daily remote phone call follow-up. Splenectomy which was present in 8/11 patients did not seem to affect the clinical course. Of note, except for the patient with myelosuppression, no increase in blood requirement was observed. When luspatercept treatment was halted in the NTDT patient, hemoglobin fell from 110 to 82 g/L, a value similar to the pre-luspatercept period. Neither death nor severe SARS or signs of cytokines storm were observed in these 11 subjects, which may be surprising, taking into account the mean age and the presence of severe comorbidities.

Our data, although preliminary, do not indicate increased severity of COVID-19 in TS. A larger number of cases needs to be collected to define the impact of this new infection and its outcome in these fragile patients.

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CONFLICT OF INTEREST

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Management of CLL patients early in the COVID-19 pandemic: An international survey of CLL experts

To the Editor:

The coronavirus disease 2019 (COVID-19) pandemic caused by the novel coronavirus (SARS CoV-2) has posed an unprecedented health emergency, especially to those with older age or comorbid medical conditions.[1] Patients with chronic lymphocytic leukemia (CLL) have a median age of about 70 years at diagnosis, and the majority suffer

from additional medical comorbidities and immunosuppressed state.[2] Therapeutic agents for CLL have immunomodulatory effects that can potentially alter the risk of contracting and the response to infection.[3,4] The interface of SARS-CoV-2 infection, severity of COVID-19 symptoms, and active treatment of CLL represents a major therapeutic dilemma—should CLL-directed therapy continue or be held? This is particularly true for patients receiving B-cell receptor kinase inhibitors, where abrupt treatment discontinuation can result in rapid decompensation in some patients that could mimic COVID-I9 symptoms. These overlapping syndromes bring forth another layer of complexity to the management of these high-risk CLL patients. Since the beginning of the COVID-19 pandemic, the CLL community has encountered many questions regarding primary prevention strategies, application of diagnostic tests for SARS CoV-2, and optimal management of CLL therapy in patients with COVID-19 illness. In the absence of clinical data guiding management of CLL in the setting of COVID-19, expert opinion is critical until ongoing and planned future studies provide high-quality data for evidence-based guidelines.

We administered a survey to a cohort of CLL experts in the United States (US), Canada, Europe, and Australia on 25 March 2020, using QuestionPro software, a cloud-based online platform (Supplementary material). The survey included questions about experts' baseline information and their recommendations on isolation, testing and CLL management in patients with CLL and COVID-19. Participants were selected from a database of physician experts chosen due to their published CLL research, and the focus of their clinical practice maintained by the CLL Society, a non-profit patient-focused and directed organization. Due to the time-sensitive nature of the topic, participants were only given 7 days to complete the online questionnaire. Descriptive results are presented in this report. Fisher's exact test was used to compare proportions of responses when applicable.

The survey was sent to 62 CLL specialists, of whom 59 responded to at least one question, and 44 completed the survey for an overall response rate of 95% and a completion rate of 71%. Most responders were from the US (76%), followed by Europe (19%), Australia (3%), and Canada (2%). Participants were clinicians or clinician/scientists (50% each) and were from academic (90%), non-academic (5%) and governmental (5%) institutions. At the time of the survey completion, 14 experts (24%) had experience taking care of at least one CLL patient with confirmed COVID-19 (7% outpatient, 10% non-intensive care unit [ICU] service, 7% ICU).

Regarding primary prevention and social distancing in patients with CLL compared to the general public, the choices and corresponding response rates were these. (a) Follow the recommendations from the World Health Organization (WHO) and the Center for Disease Control (CDC) as for the general public (32%). (b) The above plus having others do their essential chores such as grocery shopping or picking up medications (21%). (c) All the above plus refraining from even essential work if it involves contact with others (35%) and (d) All the above[1-3] plus wearing an N-95 mask and gloves if they must leave the house (12%). There were multiple general comments about the importance of total isolation of patients with CLL during the COVID-19 pandemic, especially those on active treatment or with prior treatment for CLL.

Local and federal recommendations have become stricter since the time of survey administration, making recommendations for the general public stricter and more applicable for higher-risk populations like patients with CLL. All experts who recommended using a mask pointed out the current limited supply of the N-95 masks, and advised for prioritizing their use for healthcare workers with direct exposure to COVID-19 patients. Advocates for mask use suggested utilization of surgical masks instead of an N-95 mask.

Participants were asked about their strategy for testing patients both with the current supply status (ie, limited access to the test) and at a time when the test becomes widely available. We gave experts specific scenarios for common CLL therapies, and asked for their input in patients with or without a history of multiple infections. With the current limited test availability, most experts (62%) considered offering a test to patients who call and report symptoms, while 9.5% only recommended the test for symptomatic patients during a clinic visit. Most experts did not recommend universal testing for all CLL patients in a setting where test supply is limited. No difference in response to these questions based on specific CLL therapeutics and infection history was observed (Figure S1A).

When experts were asked their advice if testing capacity were unlimited, 23% recommended universal testing for all patients. In comparison, 61% still recommended testing only for patients who call and report symptoms. More experts (38%) were in favor of universal testing for patients with a prior allogeneic stem cell transplant (Figure S1B).

We asked CLL specialists about their strategy for managing CLL-directed therapy in two patient populations with COVID-19: outpatients with mild symptoms, and inpatients (non-ICU). The response choices were: (a) holding treatment for all, (b) continuing treatment for all, (c) only continuing if there is a high likelihood of disease progression, or disease-related complications after stopping, and (d) only continuing if the CLL drug has been effective in decreasing the rate of infections in that specific patient.

For outpatients, only 14% of experts recommended unconditional continuation of CLL therapy in COVID-19 patients. Others either favored treatment discontinuation (60.5%) or continuation only based on the clinical situation (25.5%). There was a difference in the experts' approach to the management of Bruton tyrosine kinase inhibitors (BTKi) (ibrutinib and acalabrutinib) vs other treatments. For BTKi, 44% of experts favored unconditional continuation of treatment, while only 12% recommended this approach for other agents ($P < .001$). For COVID-19 inpatients (non-ICU), only 3.5% of participants elected for an unconditional continuation of CLL treatment. Again, more experts were in favor of the continuation of BTKis compared to other agents (32.5% vs 4%; $P < .001$). Details of recommendations stratified by specific CLL treatments in patients with COVID-19 in outpatient and inpatient settings are summarized in Table 1. When asked about a recommendation for IVIG use in patients with CLL and COVID-19, 72% of experts did not recommend IVIG treatment specifically for this viral infection.

TABLE 1 Expert opinion on the management of CLL therapy in patients positive for SARS-CoV-2 (n = 43)

	I would hold the drug in all patients	I would continue the drug in all patients	Would only continue if there is a high likelihood of disease progression or disease-related complications with discontinuation	Would only continue if the CLL drug has been effective in decreasing the rate of infections in that specific patient
Outpatient setting				
Ibrutinib	14%	44%	42%	0
Acalabrutinib	14%	44%	42%	0
Venetoclax	33%	23%	39%	5%
Idelalisib	60%	14%	26%	0
Duvelisib	60%	14%	26%	0
Anti CD20 antibody (monotherapy)	75%	4%	21%	0
Anti CD20 antibody (combination)	70%	5%	25%	0
Experimental therapeutics	62%	12%	24%	2%
Inpatient (non-ICU) setting				
Ibrutinib	39%	33%	26%	2%
Acalabrutinib	39%	33%	26%	2%
Venetoclax	67%	9%	19%	5%
Idelalisib	74%	5%	16%	5%
Duvelisib	79%	2%	14%	5%
Anti CD20 antibody (monotherapy)	84%	2%	12%	2%
Anti CD20 antibody (combination)	81%	2.5%	14%	2.5%
Experimental therapeutics	77%	2%	16%	5%

The CLL specialists uniformly recommended strict social isolation for patients with CLL and emphasized the importance of primary prevention. Experts had a low threshold for testing patients with CLL for SARS-CoV-2. Most favored testing patients with any levels of reported symptoms, even with limited testing availability. With unlimited access, 23% recommended universal testing of CLL patients. While most experts recommended holding CLL-directed therapy in patients with COVID-19, they seem to have a different approach to patients treated with BTKi, with more participants favoring the continuation of ibrutinib and acalabrutinib. The survey did not include questions about the rationale for recommendations, though rationale will be specifically addressed in future surveys planned by the CLL Society. Concerns about disease flare after stopping therapy may, at least in part, explain the higher interest in continuation of BTKis. Also, there is a theoretical benefit of BTKi's in blunting the hyperinflammatory stage of COVID-19 disease by targeting macrophages and/or inhibiting pro-inflammatory cytokines.[5] Alternative detrimental factors of BTKi could include diminishing humoral response to SARS-CoV-2 virus, which may be essential for long-term immunity, clearance of the virus, and protection against secondary bacterial infections. Thus, the decision to continue BTKi therapy should be weighed against the increased risk of impaired humoral immunity.

Most participants (72%) did not recommend use of IVIG in the setting of COVID-19 illness. It should be noted that this survey was performed early in the pandemic before passive antibodies in the gammaglobulin pool would be expected. Also, this recommendation does not apply to treatment with convalescent serum/immunoglobulin. Additionally, this question does not apply to patients with COVID-19 who acquire a secondary pneumonia, or patients with profound hypogammaglobulinemia.

As our understanding of the COVID-19 pandemic changes rapidly, recommendations and practices will evolve. Therefore, the presented data is most relevant to the time of this survey (April 2020). Since the administration of this survey, the American Society of Hematology (ASH) has provided an online resource for frequently asked questions about care of patients with COVID-19 in the setting of hematologic malignancies including CLL.[6] Our survey results generally align with the recommendations by the ASH expert panel. We

recognize the inherent selection bias that applies to any survey study, though our high response rate has mitigated non-response bias.

While ongoing observational and interventional studies will provide data for future evidence-based guidelines, our survey provides a snapshot of current CLL expert opinion during this rapidly evolving COVID-19 pandemic. Future surveys are planned by the CLL Society to assure an optimal approach to the management of patients with CLL during the COVID-19 pandemic.

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Special considerations in the management of patients with myelodysplastic myndrome / myeloproliferative neoplasm overlap syndromes during the SARS-CoV-2 pandemic

To the Editor:

The ongoing pandemic with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and resultant coronavirus disease 2019 (COVID-19) is resulting in high mortality and morbidity worldwide.[1,2] While the exact impact of SARS-CoV-2 in cancer patients remains to be defined, early reports, especially from China, suggest an increased mortality in those older than 60 years, those with pulmonary compromise or hematological malignancies.[3] The virus SARS-CoV-2 uses the angiotensin converting enzymes-related carboxypeptidase (ACE2) receptor to gain entry into cells, with these receptors widely expressed in the cardiopulmonary system, monocytes and monocyte-derived macrophages.[4] Monocytes and macrophages frequently interact with ACE2-expressing cells in various tissues, and ACE2 is also expressed by cells of the bone marrow (BM) niche, where it associates with the granulocyte-colony stimulating factor (G-CSF) receptor to negatively regulate hematopoietic progenitor cells mobilization (supplemental material for complete reference list in Data S1).

The cytokine profile of patients with COVID-19 resembles that of patients with secondary hemophagocytic lymphohistiocytosis (HLH), with the excess production of interleukin 2 (IL-2), IL-6, G-CSF, interferon gamma inducing protein 10, monocyte chemoattractant protein-1 and tumor necrosis factor (TNF) alpha, among others.[5,6] Severe manifestations of SARS-CoV-2 are largely cytokine mediated and include cytokine release syndrome (CRS), respiratory failure secondary to acute respiratory distress syndrome (ARDS), and multiorgan dysfunction syndrome (MODS) (Figure S1).[1,2,5] Note, IL-6 is a prominent secreted cytokine and plays a critical role in the inflammatory cascade seen.[6] This has led to the use of IL-6 and IL-6 receptor (IL-6-R)-directed monoclonal antibodies such as siltuximab (IL-6) and tocilizumab/sarilumab (IL-6-R) in the management of CRS and ARDS in patients with COVID-19.

The 2016 iteration of the World Health rganization (WHO) classification of myeloid neoplasms identifies four distinct sub-types of adult onset myelodysplastic syndromes/myeloproliferative neoplasms (MDS/MPN), namely chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia, *BCR/ABL*-negative (aCML), MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T), and MDS/MPN, unclassifiable (MDS/MPN-U).[7] Among these, proliferative variants of CMML, MDS/MPN-U and aCML tend to have persistent leukocytosis along with circulating immature myeloid cells.[8] Proliferative CMML in particular has a proinflammatory phenotype with elevated serum levels of cytokines including IL-6, TNF-alpha, monocyte colony stimulating factor (M-CSF) and IL-1RA[9]; with CMML cells demonstrating an intrinsic hypersensitivity to GM-CSF that is more prominent in RAS-mutant samples.[10] Case series have described exaggerated leukemoid reactions, CRS, ARDS and MODS in CMML patients who have undergone surgery, or in response to infections/inflammation; given the abundance of ACE2 receptors experessed on monocytes and macrophages, we hypothesize that these patients are particularly susceptible to the cytokine-related complications of SARS-CoV-2.[11]

We describe a 69-year-old man with symptomatic (constitutional symptoms), proliferative, *ASXL1*, *NRAS*, *TET2* mutated- CMML-0 with a normal karyotype, who had a stable white blood cell count (WBC) of ~35×10^9/L for 6 months, regulated on hydroxyurea. A donor search for allogenic hematopoietic cell transplant had been initiated. Further dose increments in hydroxyurea to try to better control his leukocytosis were not tolerated, due to anemia and thrombocytopenia. The patient was admitted with high grade fever and hypoxic respiratory failure to his local hospital. His WBC on admission was 90×10^9/L with neutrophilic series left-shift and he went on to develop ARDS and MODS, necessitating assisted ventilation. He was diagnosed with SARS-CoV-2 and died prior to the administration of anti-cytokine directed therapies.

Given the paucity of evidence for the management of hematological malignancies during this pandemic and the proinflammatory milieu of proliferative MDS/MPN overlap neoplasms, we formed an ad hoc expert panel to help draft consensus emergency recommendations for the management of COVID-19 in these patients. The committee also reviewed available cytokine-directed clinical trials for SARS-CoV-2 and summarized details of therapies of particular interest to patients with proliferative MDS/MPN-overlap neoplasms (Table 1).

Permissive leukocytosis in these pateints to a degree that may be reasonable in other settings may put patients at increased risk for complications in the COVID-19 era, and tighter regulation of the WBC is a worthwhile consideration. This has to be carefully balanced with the potential need for additional blood draws and clinic visits, including blood product transfusions for worsening cytopenias. In a clinically suspected case of SARS-CoV-2 in an MDS/MPN patient, frequent monitoring of CBC, with use of additional doses of hydroxyurea to control an evolving leukemoid reaction may be beneficial, though this is unclear. The use of corticosteroids as antinflammatory agents is somewhat controversial, given concerns of potentially increasing ACE-2 expression and viral replication/decreasing viral clearance, and should be used with caution. In the event of CRS or ARDS, treating