Management of CLL Patients Early in the COVID-19 Pandemic: An International Survey of CLL Experts

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ajh.25851

Financial disclosures

Brian Koffman: Consultation: Abbvie, Astra Zeneca, Janssen, Novartis, Verastem. Speakers Bureau: Bristol Myers Squibb, Celgene, TG Therapeutics

Anthony Mato: holds a consultancy role for TG Therapeutics (in addition DSMB), Abbvie, Pharmacyclics, Johnson & Johnson, Regeneron, Astra Zeneca, Genentech, LOXO, and Celgene and has received research funding from TG Therapeutics, Abbvie, Pharmacyclics, Johnson & Johnson, Regeneron, Genentech, LOXO, Portola, DTRM, and Acerta.

John C. Byrd: Clinical trial research funding from Acerta, Pharmacyclics, and Celgene. Consultation Astra Zeneca, Acerta, Janssen Oncology, Pharmacyclics, and Verastem. Dr. Byrd is supported by the National Cancer Institute (R35 CA198183, JCB)

Alexey Danilov: has received research funding from Astra Zeneca, Gilead Sciences, Genentech, Aptose Biosciences, MEI Pharma, Takeda Oncology, Bayer Oncology, Verastem Oncology and Bristol-Meyers-Squibb; honoraria from Astra Zeneca, Celgene, Curis, Genentech, Gilead Sciences, Janssen Oncology, Pharmacyclics, Seattle Genetics, TG Therapeutics and Verastem Oncology. AVD is a Leukemia and Lymphoma Society Scholar in Clinical Research.

Brad Hedrick:none

Chaitra Ujjani: Abbvie, Pharmacyclics, Gilead, Genentech, Verastem, Atara, Astrazeneca

Lindsey Roeker:Research funding from American Society of Hematology, minority ownership interest in Abbvie and Abbott Laboratories

Deborah Stephens:Consulting fees from Pharmacyclics and Jannsen. Research funding from Acerta, Gilead, Karyopharm, Juno, Verastem. Honoraria from Genentech.

Matthew Davids: Personal fees from AbbVie, Adaptive Biotechnologies, Ascentage Pharma, AstraZeneca, Beigene, Celgene, Genentech, Gilead Sciences, Janssen, MEI Pharma, Pharmacyclics, Research to Practice, Syros Pharmaceuticals, TG Therapeutics, and Verastem, and institutional research funding from Astra-Zeneca, Ascentage Pharma, Genentech, MEI Pharma, Pharmacyclics, Surface Oncology, TG Therapeutics and Verastem, outside the submitted work.

John Pagel : Holds a consultancy role for TG Therapeutics, Pharmacyclics, Astra Zeneca, Lily, and Gilead.

Mazyar Shadman: Consultation and Advisory Boards: Abbvie, Genentech, Astra Zeneca, Sound Biologics, Pharmacyclics, Verastem, ADC Therapeutics, Cellectar, Bristol Myers Squibb and Atara Biotherapeutics. Research Funding: Mustang Bio, Celgene, Bristol Myers Squibb , Pharmacyclics, Gilead, Genentech, Abbvie, TG Therapeutics, Beigene, Astra Zeneca, Sunesis, Acerta Pharma, Beigene and Merck

This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

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 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 March 25, 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 seven 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: 1-Follow the recommendations from the World

Health Organization (WHO) and the Center for Disease Control (CDC) as for the general public (32%), 2- The above plus having others do their essential chores such as grocery shopping or picking up medications (21%), 3- All the above plus refraining from even essential work if it involves contact with others (35%), and 4- All the above (1,2,3) 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 (i.e., 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 . (supplement Figure 1A)

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. (supplement Figure 1B)

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: 1) holding treatment for all, 2) continuing treatment for all, 3) only continue if there is a high likelihood of disease progression or disease-related complications after stopping, and 4) only continue 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) versus other treatments. For BTKi, 44% of experts favored unconditional continuation of treatment, while only 12% recommended this approach for other agents; ($p < 0.0001$) 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%; $p < 0.0001$). 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

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 protectional 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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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%