COVID-19 in patients with CLL: improved survival outcomes and update on management strategies

Short Title: COVID-19 in patients with CLL

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Word count: 1504

Tables/Figures: 1 Table, 1 Figure

Supplemental Figures/Tables: 3 Tables, 1 Figure

References: 24

With enhanced testing availability and evolution of therapeutic strategies, survival of COVID-19 infected patients has improved over time.[1-3] Two large series reported outcomes for patients with chronic lymphocytic leukemia (CLL) infected with COVID-19 from February to May 2020, reporting case fatality rates (CFR) of 31-33%.[4,5] Whether CLL patients have experienced improvement in outcomes over time as observed in the general population remains unknown. To understand change in outcomes over time, we present this follow up study, which builds upon a previously reported cohort with extended follow up and addition of more recently diagnosed cases.

Several agents have been granted emergency use authorization for treatment of COVID-19 by the FDA,[6-9] and dexamethasone demonstrated an overall survival (OS) benefit for COVID-19 infected patients requiring oxygen.[10,11] These therapeutic studies have included few patients with hematological malignancies; disease specific outcomes have not been presented. Given possible differences in immune response and risk of infection, understanding the benefit of these therapies in a CLL-specific population is crucial.

Early data from a small series suggest that CLL patients may not consistently mount anti-SARS-CoV-2 antibodies following infection.[12] This finding along with previous reports of inadequate response to other vaccines in patients with CLL[13-19] highlight significant questions regarding COVID-19 vaccine efficacy in this population.

In this retrospective study, investigators from 45 centers identified patients with CLL diagnosed with COVID-19 based on PCR detection of SARS-CoV-2 between 2/17/2020 and 2/1/2021. Institutional review board approvals were granted. The study was conducted in accordance with Declaration of Helsinki.

A uniform case report form was utilized to collect baseline demographics, comorbidities, CLL-directed treatment history, date of COVID-19 diagnosis, as well as COVID-19 clinical course and management strategy. Information regarding anti-SARS-CoV-2 serology testing performed through routine care was collected if performed; specific antibody tested was not mandated or recorded.

Our primary aim was to report CFR for a larger group of patients with CLL diagnosed with COVID-19 with longer follow up. We further aimed to report CFR stratified by date ("early cohort" diagnosed 2/17/2020-4/30/2020 and "later cohort" diagnosed 5/1/2020-2/1/2021; dates selected to mirror population-based studies[1,2]), examine outcomes for patients who received specific COVID-19 directed therapies, and describe serology testing results for those tested in routine clinical care.

OS was estimated using the Kaplan-Meier method.[20] Univariable analyses adjusted for potential confounders to evaluate relationship between baseline characteristics and COVID-19 directed therapies and OS utilizing Cox regression were performed. Analyses were performed using Stata 16.[21]

This analysis included 374 patients with CLL diagnosed with COVID-19. With median follow-up of 38 days (range 1-364 days) and 63.5 days for survivors (range 1-364), the CFR is 28%. Hospital admission was required for 75% and ICU admission was required for 27%. Supplemental oxygen was used for 68% and mechanical ventilation was required for 20%. For patients who required hospital admission, the CFR was 36% (99/278), while CFR was 4.3% (4/92) in those who were not admitted. Age >75 years and cumulative illness rating scale-geriatric (CIRS)[22] > 6 were independent predictors of poor survival. Sex, hypogammaglobulinemia, and CLL-directed treatment (including history of any treatment, current

treatment, current BTK inhibitor therapy, and prior lines of therapy) were not associated with survival (**Supplemental Table 1**).

To examine trends over time, we compared updated data for 254 patients diagnosed between 2/17/2020 and 4/30/2020 (early cohort) to 120 patients more recently diagnosed between 5/1/2020 and 2/1/2021 (later cohort). Comparison of baseline characteristics and markers of COVID-19 severity in these two cohorts are presented in **Table 1**. A larger proportion of patients in the early cohort were admitted (85% vs. 55%) and required ICU admission (32% vs. 15%). CFR in the early cohort was 35% vs. 11% in the later cohort (p<0.001). For patients requiring hospitalization, CFR was 40% (86/213) in the early cohort and 20% (13/65) in the later cohort (p=0.003). For those who required oxygen, CFR was 44% vs. 25% (p=0.015). The proportion of hospitalized patients requiring ICU level care was lower in the later cohort (37% in early cohort vs. 29% in later cohort), while CFR has remained high for the subset of patients who require ICU level care (52% vs. 50%, p=0.89). Difference in management for BTKi-treated patients was observed in early vs. later cohorts. In the early cohort, 76% of patients on BTKi had their drug held or discontinued. In the later cohort, only 20% of BTKi-treated patients held of discontinued this therapy.

Univariable analyses examined associations between administration of specific COVID-19 therapies and OS in all admitted patients and also the subset of admitted patients who required supplemental oxygen (**Supplemental Tables 2 and 3**). Remdesivir (HR 0.48, p=0.03) and convalescent plasma (HR 0.50, p=0.04) administration were associated with improved OS, while admitted patients who received corticosteroids (HR 1.73, p=0.01) and hydroxychloroquine (HR 1.53, p=0.04) had an increased risk of death.

Supplemental Table 4 describes baseline characteristics and COVID-19 course for those who did vs. did not receive corticosteroids. Corticosteroids were associated with increased risk of death when controlled for admission status (HR 1.8, 95% CI 1.2-2.7 p= 0.007) and need for mechanical ventilation (HR 2.0, 95% CI 1.3–3.1, p=0.002), though not significantly associated with survival when controlled for supplemental oxygen requirement (HR 1.4, 95% 0.93-2.2, p=0.11). Further, admitted patients treated with corticosteroids in the later cohort did not experience OS benefit (HR 2.6, 95% 0.6-11.9, p=0.22). Secondary infections were observed in 26% (18/69) vs. 8% (12/154) of those who did vs. did not receive corticosteroids and 26% (26/99) vs. 8% (6/75) of admitted patients who required oxygen and did vs. did not receive corticosteroids.

Following acute infection, COVID-19 serology was checked in 25% of patients (93/374). Of patients tested, serology result was positive in 60%, negative in 39%, and equivocal in 1%. The proportion of untreated patients, patients treated with BTKi, treated with Venetoclax, and with hypogammaglobulinemia who developed anti-SARS-CoV-2 antibodies were 74% (29/39), 48% (12/25), 30% (3/10), and 60% (14/28), respectively.

Since CLL patients diagnosed with COVID-19 in spring 2020 experienced high CFR (31-33%),[4,5] we aimed to examine CFR in a larger cohort with additional follow up and with a subset of patients diagnosed later in the course of the pandemic. Our findings mirrored population-based studies[1-3] with falling CFR (35% in those diagnosed before 5/1/2020 vs. 11% in those diagnosed after 5/1/2020). Improvement in OS was also observed in hospitalized patients and those who require supplemental oxygen, and the proportion of hospitalized patients requiring ICU level care has fallen, suggesting that patients in the later cohort are experiencing a less severe clinical course, and the observed difference in CFR over time may not just be due to more frequent testing and identification of less symptomatic patients.

While our data corroborate prior studies demonstrating benefit of remdesivir[6] and lack of benefit for hydroxychloroquine,[23] we interestingly found OS benefit associated with convalescent plasma[24] and lack of benefit (significantly inferior OS in admitted patients) with corticosteroids.[10] Regarding convalescent plasma, patients with CLL have known humoral immunodeficiency, and antibody-based therapies may uniquely benefit this population. The RECOVERY trial demonstrated OS benefit for dexamethasone in COVID-19 patients requiring oxygen (HR 0.82, 95% CI 0.72-0.94) and mechanical ventilation (HR 0.64, 95% CI 0.51-0.81).[10] In contrast, corticosteroid use was associated with a trend toward inferior OS in patients requiring oxygen and significant risk of death for intubated CLL patients. Use of corticosteroids in the earlier cohort may have been reserved for patients with more severe disease, as data regarding use of corticosteroids in COVID-19 were not yet available. Thus, inferior outcomes for steroid treated patients in this cohort may be an artifact of their use in patients with more severe cases. As RECOVERY trial data were published 7/2020, we hypothesized that patients in the later cohort were more likely to receive corticosteroids in a data-driven, optimal clinical setting. Despite this, corticosteroid use was not associated with improved OS in the later cohort. While use of corticosteroids was non-randomized and potentially biased by clinical context, these data are hypothesis generating and suggest that COVID-19 directed interventions, particularly immunomodulatory agents, require prospective study specifically in immunocompromised populations. While these data are not sufficient to change recommendation for use of corticosteroids given demonstrated benefit in a prospective clinical trial, they do raise question about the benefit of immunomodulatory or immunosuppressive therapy in a population at increased risk of infection, as demonstrated in CLL-directed therapeutic trials.

Finally, this multicenter series was consistent with a prior single center study,[12] and 60% of CLL patients developed positive anti-SARS-CoV-2 serology testing following PCR diagnosis of COVID-19. This is the largest reported series of serologic testing for patients with CLL and adds further evidence that antibody production following COVID-19 is not uniform in patients with CLL. Coupled with prior reports of decreased responses to other vaccines,[13-19] further study is ongoing to understand immune response to SARS-CoV-2 vaccination in CLL patients.

Reassuringly, the overall trend in CFR for CLL patients mirrors improved OS observed for patients with COVID-19 in the general population, though these data highlight opportunities for further investigation into optimal management of COVID-19, immune response following infection, and effective vaccination strategy for CLL patients.

Acknowledgements: This research was supported in part by the NIH/NCI Cancer Center Support Grant P30 CA008748. LER recognizes support from the American Society of Hematology Research Training Award for Fellows outside of the submitted work. IEA receives research support from the Intramural Program of the National Heart, Lung, and Blood Institute and American Society of Hematology Scholar Award. TAE recognizes support from the Oxford NIHR Biomedical Research Centre.

Authorship Contributions: LER: Co-PI, study design, data collection, coordination, analysis, and interpretation, manuscript writing; TAE: study design, site coordination, data collection and interpretation, manuscript writing and editing; MCT, NL, AC, MSD, POB, LL, KAR, JNA, RC, ALG, DA, JMP, NMC, JAGM, JAHR, RM, CCC, AO, ANS, JLJ, MRW, DES, DW, TM, SV, ES, PMB, JP, PEMP, GFP, SFH, HP, SS, AS, MK, RJ, HW, RW, AB, SL, KMI, IEA, CSU, SS, EAC: : data collection and interpretation, manuscript editing; ARM: ARM: Study PI, study design, data collection, coordination, analysis, and interpretation, manuscript writing.

Conflict of Interest: LER has served as a consultant for AbbVie, AstraZeneca, Pharmacyclics, Vaniam group, and Verastem, holds minority ownership interest in Abbott Laboratories, and has received research funding from Pfizer outside of the submitted work. TAE has received honorarium/advisory board honorarium from Roche, Gilead, KITE, Janssen, AbbVie, AstraZeneca, LOXO Oncology, Beigene, and Incyte, receives research support from Gilead and AstraZeneca, has received travel support from Gilead, Takeda, and AbbVie, and served on a trial steering committee for LOXO Oncology. MCT has received honoraria from MJH Life Sciences, VJ Heme Onc, Curio Science. NL reports grants from Loxo Oncology, grants and personal fees from, and consultancy, board of directors, or advisory for AbbVie, AstraZeneca, BeiGene, and Genentech, personal fees from and consultancy, board of directors, or advisory committees for Celgene, Gilead, Janssen, and Pharmacyclics; and grants from Juno, Octernal, Verastem, TG Therapeutics, MingSight, and Octapharma, outside the submitted work. MSD reports grants and personal fees from AbbVie, Ascentage Pharma, BMS, Genentech, MEI Pharma, Novartis, Pharmacyclics, Takeda, TG Therapeutics, Verastem, and AstraZeneca, personal fees from Adaptive Biotechnologies, BeiGene, Celgene, Eli Lilly, Gilead Sciences, Janssen, Merck, Research to Practice, Syros Pharmaceuticals, and personal fees from Zentalis; and grants from Surface Oncology, outside the submitted work. LL has served on speaker's bureaus for Seattle Genetics, Celgene/BMS, KitePharma, BeiGene, Pharmacyclics/Janssen, AstraZeneca, and has participated in advisory boards for Bayer, Seattle genetics, ADC therapeutics, Abbvie, Janssen, Pharmacyclics, Kite, AstraZeneca. KAR receives research funding from Genentech, AbbVie, Janssen, and Novartis, has consulted for Acerta Pharma, Genentech, Abbvie, Pharmacyclics, Innate Pharma, and AstraZeneca, and received travel funding from AstraZeneca. JNA has received research funding from Genentech, Janssen, and Celgene, and has served as a consultant to Pharmacyclics, AbbVie, Genentech, AstraZeneca, Sunesis, and Janssen. RC serves as a speaker for Roche, Janssen, BMS, Abbvie, Takeda, serve on advisory boards for Janssen, Celgene, Abbvie, Servier, Kyowa-Kirin, Takeda, and has received travel funding from Roche, Pfizer, Janssen, Celgene, Abbvie, Servier, and Takeda. JMP reports consultancy with Loxo Oncology, AstraZeneca, Gilead, and BeiGene. JAGM has held a consulting or advisory role for AbbVie, Astra-Zeneca, Janssen, Roche, received research funding from AbbVie, Janssen, and has received speakers fees from AbbVie, Astra-Zeneca, Janssen. JAHR serves as a consultant for Janssen, Abbvie, Roche, Gilead, Celgene, Amgen, Takeda, is on the speaker's bureau for Janssen, Abbvie, Roche, Gilead, Celgene, AstraZeneca, Amgen, Takeda, Beigene, and receives grants/research support from Celgene. CCC reports personal fees from Loxo Oncology, Novartis, AbbVie, Genentech, MEI Pharma, and Octapharma, and payment to her institution for clinical trials from Loxo oncology, Gilead, H3 Biomedicine, and Incyte. AO receives grants for academic research from Beigene, Kancera, holds stock ownership in Kancera, and has served as a consultant for Sanofi. SM served as a consultant or advisor for AstraZeneca, BeiGene, Genentech,

Pharmacyclics, and Verastem, served on the speaker's bureau for AstraZeneca, BeiGene, Janssen, and Pharmacyclics, and received research funding from AbbVie, AstraZeneca, BeiGene, Juno, Loxo, Novartis, Pharmacyclics, and TG Therapeutics. PMB has consulted for PCYC/AbbVie, Genentech, Gilead, Merck, Seattle Genetics, Verastem, AstraZeneca, Celgene, and Morphosys. PEMP serves as a consultant for AbbVie, AstraZeneca, Atura, Gilead, Janssen, Novartis, Roche, and Tolero Pharmaceuticals, has been a remunerated speaker for AbbVie, AstraZeneca, Gilead, Janssen, Novartis, and Roche, has received travel support from AbbVie, Gilead, Janssen, Novartis, and Roche, and has received research funding from Gilead and Roche. SFH has served as a consultant for Celgene, Bayer, Genentech, Pharmacyclics, Novartis, AbbVie, received research funding from DTRM Biopharm, Celgene, TG Therapeutics. SS served as a consultant for Janssen and received research support from Lymphoma Research Foundation. AS has served as a consultant for TG Therapeutics, Alexion, Jazz Pharmaceuticals, Pharmacyclics, AstraZeneca, Janssen, Celgene, Abbvie, Genentech, Kite Pharma, Novartis, and is on the speakers bureau for TG Therapeutics, Alexion, Jazz Pharmaceuticals, Pharmacyclics, AstraZeneca, Janssen, Celgene, Abbvie, Genentech, Kite Pharma, BeiGene, Verastem, Seattle Genetics. MK has served as a consultant for AZD, Celgene and Pharmacyclics and is on the speaker's bureau for Seattle genetics. RW reports receiving travel support and serving on speaker's bureau for Abbvie, Janssen, and Gilead. AB reports receiving travel support and serving on speaker's bureau for Gilead. CSU has consulted for Pharmacyclics, Abbvie, Astrazeneca. MS received research funding from Mustang Bio, Celgene, Pharmacyclics, Gilead, Genentech, Abbvie, TG therapeutics, Beigene, Acerta Pharma, Merck, and has served on advisory boards or as a consultant for Abbvie, Genentech, Astra Zeneca, Sound Biologics, Verastem, ADC therapeutics, BMS and Atara Biotherapeutics. EAC serves on advisory boards for Novartis, Tessa, BMS, and KITE pharma, and receives research funding from Lymphoma Research Foundation. ARM has served as a consultant for Celgene, Acerta, and Janssen; has served as a consultant for and received research funding from AbbVie, Loxo, Genentech, Pharmacyclics, AstraZeneca, Sunesis, and Johnson & Johnson; has received research funding from DTRM Biopharma and Gilead; and has served as a consultant for, received research funding from, is a DSMB member, and other for TG Therapeutics. All other authors report no conflict of interest.

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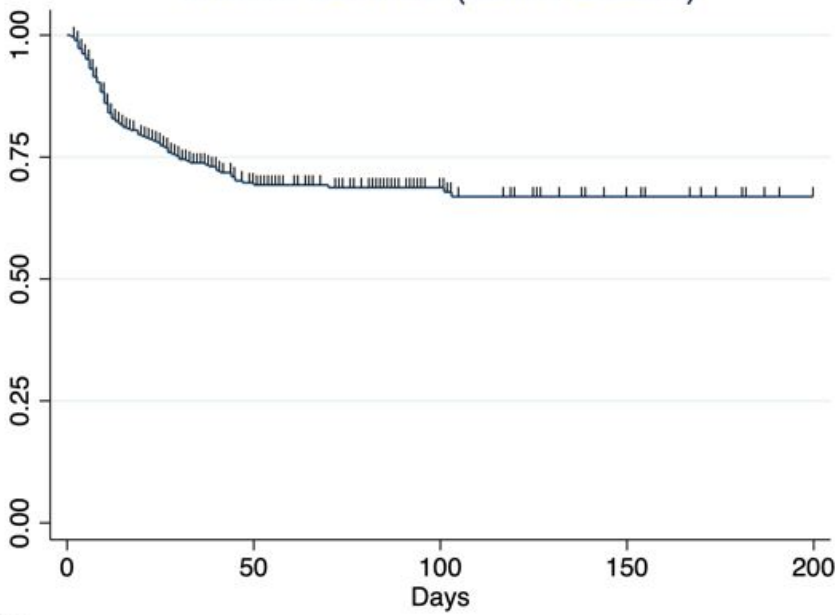
Table 1. Baseline characteristics and COVID-19 management.

	Early Cohort (n=254)		Later Cohort (n=120)		Entire cohort (n=374)	
	Proportion, unless otherwise specified	**Number with available data**	**Proportion, unless otherwise specified**	**Number with available data**	**Proportion, unless otherwise specified**	**Number with available data**
Baseline Characteristics						
Age at CLL diagnosis, median in years (range)	62.5 (31 - 92)	248	59 (29-86)	119	61 (29-92)	367
Age at COVID-19 diagnosis, median in years (range)	70 (36 - 98)	254	65.5 (29-93)	120	68 (29-98)	374
Male	64%	254	65%	120	64%	374
White	86%	249	85%	116	85%	365
CIRS,[22] median (range)	8 (4-32)	229	8 (4-21)	117	8 (4-32)	346
CLL treatment history		253		119		372
Never treated	44%		47%		45%	
Prior therapy	56%		53%		55%	
Lines of therapy for previously treated patients, median (range)	1.5 (1-8)	136	1 (1-7)	61	1 (1-8)	197
Receiving therapy at time of COVID-19 diagnosis	39%	254	34%	119	38%	373
Receiving BTK inhibitor at time of COVID-19 diagnosis	29%	253	21%	119	26%	372
Receiving Venetoclax at time of COVID-19 diagnosis	8%	253	9%	119	8%	372
COVID-19 Management						
Admitted	85%	252	55%	119	75%	371
ICU Admission	32%	250	15%	107	27%	357
Imaging Performed	89%	245	60%	108	80%	353
Pneumonia on Imaging	88%	224	62%	82	81%	306
Supplemental Oxygen	78%	250	45%	112	68%	362
Mechanical Ventilation	25%	246	9%	111	20%	357
Steroids Administered	42%	244	39%	112	41%	356

BTK: Bruton Tyrosine Kinase; CIRS: cumulative illness rating scale.

Figure 1. Overall survival from the time of COVID-19 diagnosis of (A) the entire cohort and (B) stratified by timing of diagnosis for patients who required oxygen

A.



Number at risk

370	160	84	57	45

B.