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Letter to Blood

TO THE EDITOR:

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

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With enhanced testing availability and evolution of therapeutic strategies, survival of COVID-19–infected patients has improved over time.[1-3] Two large series have reported outcomes for patients with chronic lymphocytic leukemia (CLL) infected with COVID-19 from February through May 2020, reporting case fatality rates (CFRs) of 31% to 33%.[4,5] Whether patients with CLL have experienced improvement in outcomes over time, as observed in the general population, has remained 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.

Emergency use authorization has been granted by the US Food and Drug Administration for several agents for treatment of COVID-19,[6-9] and dexamethasone has 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, and disease-specific outcomes have not been presented. Given the 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 patients with CLL may not consistently generate anti-SARS-CoV-2 antibodies after infection.[12] This finding, along with previous reports of inadequate response to 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 polymerase chain reaction detection of SARS-CoV-2 from 17 February 2020 through 1 February 2021. Institutional review board approvals were granted, and the study was conducted in accordance with the Declaration of Helsinki.

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

Our primary purpose was to report the CFR for a larger group of patients with CLL who were diagnosed with COVID-19 and had a longer follow-up. We further sought to report the CFR stratified by date (the "early cohort," diagnosed from 17 February through 30 April 2020 and the "later cohort," diagnosed from 1 May 2020 through 1 February 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 Cox regression analyses adjusted for potential confounders were performed (Stata, v 6[21]) to evaluate the relationship between baseline characteristics and COVID-19–directed therapies and OS.

This analysis included 374 patients with CLL who were diagnosed with COVID-19. With median follow-up of 38 days (range, 1-364 days) for the entire group and 63.5 days for survivors (range, 1-364), the CFR was 28%. Hospital admission was required for 75%, and intensive care unit (ICU) admission was required for 27%. Supplemental oxygen was used for 68% of the patients and mechanical ventilation was necessary for 20%. For patients who were admitted to the hospital, the CFR was 36% (99 of 278), whereas it was 4.3% (4 of 92) for 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 a history of any treatment, current treatment, current Bruton tyrosine kinase inhibitor (BTKi) therapy, and prior lines of therapy) were not associated with survival (supplemental Table 1, available on the *Blood* Web site).

To examine trends over time, we compared updated information for 254 patients diagnosed from 17 February through 30 April 2020 (early cohort) to data for 120 patients more recently diagnosed from 1 May 2020 through 1 February 2021 (later cohort). Comparison of baseline characteristics and markers of COVID-19 severity in these 2 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%). The CFR in the early cohort was 35% vs 11% in the later cohort ($P < .001$). For patients requiring hospitalization, the CFR was 40% (86 of 213) in the early cohort and 20% (13 of 65) in the later cohort ($P = .003$). For those who required oxygen, the CFR was 44% vs 25% ($P = .015$). The proportion of hospitalized patients requiring ICU-level care was lower in the later cohort (37% in early cohort vs 29% in the later cohort), whereas the CFR remained high for the subset of patients who required ICU-level care (52% vs 50%; $P = .89$). A difference in management of BTKi-treated patients was observed in the early vs the later cohort. In the early cohort, 76% of patients receiving BTKi had their drug therapy suspended or discontinued. In the later cohort, only 20% of BTKi-treated patients had their therapy suspended or discontinued.

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 (hazards ratio [HR], 0.48; $P = .03$) and convalescent plasma (HR, 0.50; $P = .04$) administration were associated with improved OS, whereas admitted patients who received corticosteroids (HR, 1.73, $P = .01$) and hydroxychloroquine (HR, 1.53; $P = .04$) had an increased risk of death.

Supplemental Table 4 describes baseline characteristics and the COVID-19 course for those who did vs did not receive corticosteroids. Corticosteroids were associated with increased risk of death when the data were adjusted for admission status (HR, 1.8; 95% confidence interval [CI], 1.2-2.7; $P = .007$) and the need for mechanical ventilation (HR, 2.0; 95% CI, 1.3-3.1; $P = .002$), although they were not significantly associated with survival when the data were adjusted for use of supplemental oxygen (HR, 1.4; 95% CI, 0.93-2.2; $P = .11$). Furthermore, admitted patients treated with corticosteroids in the later cohort did not experience an OS benefit (HR, 2.6; 95% CI ,0.6-11.9; $P = .22$). Secondary infections were observed in 26% (18 of 69) vs 8% (12 of 154) of those who did vs did not receive corticosteroids and in 26% (26 of 99) vs 8% (6 of 75) of admitted patients who required oxygen and did vs did not receive corticosteroids.

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

Because the CFR of patients with CLL who were diagnosed with COVID-19 in the spring of 2020 was high (31% to 33%),[4,5] we wanted to examine the CFR in a larger cohort with additional follow-up and in a subset of patients diagnosed later in the course of the pandemic. Our findings mirrored population-based studies[1-3] with decreasing CFR (35% in those diagnosed before 1 May 2020 vs 11% in those diagnosed after that date). Improvement in OS was also observed in hospitalized patients and in those who required supplemental oxygen, and the proportion of hospitalized patients who needed ICU-level care declined. These trends suggest that patients in the later cohort experienced a less severe clinical course and that the observed difference in CFR over time may not just be due to more frequent testing and identification of less symptomatic patients. (Figure 1).

Although our data corroborate prior studies that demonstrated the benefit of remdesivir[6] and the lack of benefit of hydroxychloroquine,[23] we interestingly found an OS benefit associated with convalescent plasma[24] and a 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 an OS benefit of 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 a significant risk of death for intubated patients with CLL. 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 disease. As RECOVERY trial data were published in July 2020, we hypothesized that patients in the later cohort were more likely to receive corticosteroids in a data-driven, optimal clinical setting. However, corticosteroid use was not associated with improved OS in the later cohort. Although the use of corticosteroids was nonrandomized and is potentially biased by clinical context, the data are hypothesis generating and suggest that COVID-19 directed interventions, particularly immunomodulatory agents, require prospective study, specifically in immunocompromised populations.

Table 1. Baseline characteristics and COVID-19 management

	Early cohort (n = 254)		Later cohort (n = 120)		Entire cohort (N = 374)	
	Proportion, unless otherwise specified, %	Patients with available data, n	Proportion, unless otherwise specified, %	Patients with available data, n	Proportion, unless otherwise specified, %	Patients with available data, n
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

CIRS, cumulative illness rating scale.

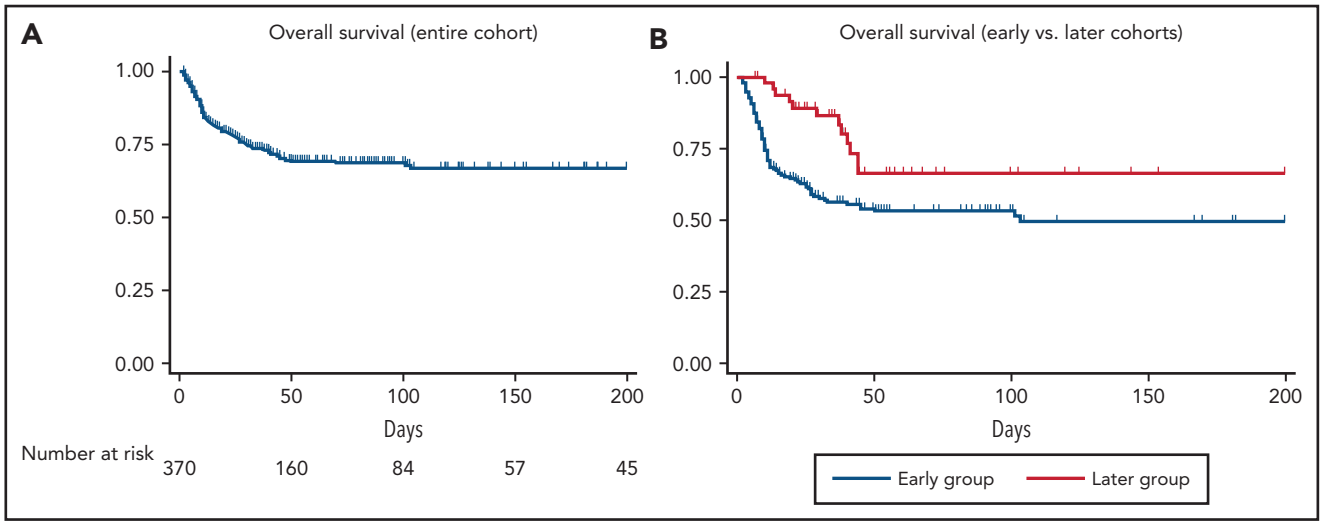

Figure 1. Overall survival from the time of COVID-19 diagnosis. The entire cohort (A) and stratified by timing of diagnosis (B) for patients who required oxygen.

Although these data are not sufficient to change recommendations for the use of corticosteroids given the demonstrated benefit in a prospective clinical trial, they raise a 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, our multicenter series was consistent with a prior single-center study,[12] and 60% of patients with CLL developed positive anti-SARS-CoV-2 serology results after polymerase chain reaction diagnosis of COVID-19. That study is the largest reported series of serologic testing for patients with CLL and adds further evidence that antibody production after 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 gain understanding of the immune response to SARS-CoV-2 vaccination in patients with CLL.

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

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Authorship

Contribution: L.E.R. was a joint senior principal investigator, responsible for the study design, and data collection, coordination, analysis, and interpretation and writing the manuscript; T.A.E. assisted with the study design, site coordination, data collection and interpretation, and writing and editing the manuscript; M.C.T., N.L., A.R.C., M.S.D., P.O.B., L.L., K.A.R., J.N.A., R.C., A.L.-G., D.A., J.M.P., N.M.-C., J.A.G-.M., J.-A.H.-R., F.M., C.C.C., A.Ö., L.H., A.N.S., J.L.J., M.R.W., D.E.-S., D.W., S.M., T.M., S.V., E.S., P.M.B., J.P., P.E.M.P., G.F.P., S.F.H., H.P., S. Sundaram, A.S., M.K., R.J., H.W., R.W., A.B., S.L., K.M.I., C.A.P., I.E.A., C.S.U., M.S., S. Skånland, and E.A.C. were involved in data collection and interpretation and edited the manuscript; A.R.M. was a joint senior principal investigator and was responsible for study design and data collection, coordination, analysis, and interpretation and writing the manuscript.

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Footnotes

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Original data are available by e-mail request to the corresponding author.

The online version of this article contains a data supplement.

There is a *Blood* Commentary on this article in this issue.

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TO THE EDITOR:

Torque teno mini virus as a cause of childhood acute promyelocytic leukemia lacking PML/RARA fusion

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The treatment of patients with acute promyelocytic leukemia (APL) can serve as a paradigm for cancer therapy.[1] The outcome of this disease, in adults and in children, has significantly improved with the introduction of target-specific agents, such as all-trans retinoic acid (ATRA) and arsenic trioxide (ATO), providing long-term survival for most patients.[2,3] Although morphologic and clinical suspicion is sufficient to immediately initiate ATRA, definitive diagnosis relies on the demonstration of *PML/RARA* translocation, on alternative *RARA* rearrangements represented by *RARA* gene fusion to other partners, cryptic insertion into the *PML* gene, or vice versa that altogether occur in more than 98% of APL cases.[4-6] Here we describe an even more challenging situation where all conventional diagnostic approaches failed to detect an oncogenic event associated with the diagnosis of APL.

A 6-year-old girl was admitted to the emergency department with a 3-day history of shoulder pain and fever. On physical examination, she presented with pallor and ecchymosis of the lower limbs. A full blood count showed a hemoglobin concentration of 9.7 g/dL, and leukocyte and platelet counts of $2.8 \times 10^3/\mu L$ and $101 \times 10^3/\mu L$, respectively. Coagulation tests showed consumptive coagulopathy with slightly prolonged prothrombin and activated partial thromboplastin times, an increased D-dimer concentration, and hypofibrinogenemia. A peripheral blood smear showed atypical promyelocytes packed with numerous azurophilic granules (Figure 1A), whereas analysis of the bone marrow aspirate demonstrated markedly hypercellular marrow containing 85% abnormal promyelocytes with Auer rods ($CD33^+$, $CD13^+$, $CD38^+$, $CD99^+$, $HLA\text{-}DR^{low}$), with strong and diffuse reactivity to