anti-HPA-1a monoclonal antibody in mice: toward targeted treatment of fetal-alloimmune thrombocytopenia. *Blood*. 2013;122(3):321-327.

6. Ghevaert C, Wilcox DA, Fang J, et al. Developing recombinant HPA-1a-specific antibodies with abrogated Fcgamma receptor binding for the treatment of fetomaternal alloimmune thrombocytopenia. *J Clin Invest*. 2008;118(8):2929-2938.

7. Zhi H, Ahlen MT, Skogen B, Newman DK, Newman PJ. Preclinical evaluation of immunotherapeutic regimens for fetal/neonatal alloimmune thrombocytopenia. *Blood Adv*. In press.

8. Bussel JB, Vander Haar EL, Berkowitz RL. New developments in fetal and neonatal alloimmune thrombocytopenia. *Am J Obstet Gynecol*. In press.

DOI 10.1182/blood.2021012454

LYMPHOID NEOPLASIA

Comment on Roeker et al, page 1768

COVID-19 in patients with CLL: how can we change the odds?

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In this issue of *Blood*, Roeker et al[1] report an updated analysis of an international, multicenter study on the outcomes of 374 patients with chronic lymphocytic leukemia (CLL) diagnosed with COVID-19. The current analysis evaluated the case fatality rate in an expanded cohort with a longer follow-up period and compared outcomes over time. They found that overall case fatality rate remained high (28%). However, it appeared to have dropped from 35% in an early cohort, diagnosed before May 2020, to 11% in a later cohort, diagnosed after May 2020. Interestingly, an overall survival benefit was observed in patients treated with remdesivir and convalescent plasma.

CLL typically affects elderly patients, many with numerous comorbidities. It is commonly accompanied by profound immune dysregulation, related to CLL itself and/or to anti-CLL therapy. The mechanisms underlying the immunodeficiency in CLL include quantitative and qualitative defects in cell-mediated immunity, the complement system, neutrophil and phagocytic function, and antibody production, which are evident at diagnosis and worsen during disease course.[2] Infections are the main cause of death in patients with CLL.[2] Hence, it is not surprising that patients with CLL have an increased risk for severe disease as well as mortality from COVID-19. In a previous report by the European Research Initiative on CLL (ERIC) and CLL Campus, mortality rate in 190 patients with CLL hospitalized with COVD-19 appeared similarly high, reaching 32.5%.[3] In a meta-analysis of 3377 predominantly hospitalized patients, with various hematologic malignancies (including CLL) and COVID-19, the risk of death was 34%, and age was strongly associated with mortality.[4] Recent systemic anticancer therapy did not increase the risk of death.[4] In the ERIC study[3] as well as in the study by Roeker et al, data were retrospectively collected on patients diagnosed with symptomatic COVID-19, confirmed by polymerase chain reaction (PCR) detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The fatality rate in this setting may have been overestimated, as more severe cases were more likely to be included. Asymptomatic patients and those with mild symptoms who were not PCR confirmed may not have been included.

The prominent reduction in mortality from 35% in patients diagnosed before May 2020 ("early cohort") to 11% in patients diagnosed afterward ("later cohort") is encouraging and intriguing.[1] One explanation is that the later cohort included a larger proportion of patients with mild symptoms who were diagnosed because of increased awareness of COVID-19 and more extensive screening to detect SARS-CoV-2 over time. That is supported by the lower hospitalization rates and lower rates of hospitalized patients requiring intensive care unit (ICU) care in the later cohort. Another possibility is better patient management owing to increasing experience, expanding therapeutic options, and improved capacity of health systems to manage an influx of patients.

The current therapeutic strategies in the management of COVID-19 include 3 modalities: antiviral agents, to prevent viral replication; immunomodulators, to attenuate the dysregulated host immune response accompanying severe disease; and thromboprophylaxis, to mitigate against the predisposition of a hypercoagulability state in patients with COVID-19. Among the anti–COVID-19 therapies given to patients with CLL and analyzed in this study,[1] only remdesivir and convalescent plasma were shown to improve survival, whereas corticosteroids and hydroxychloroquine had been associated with an increased risk of death. Remdesivir, an antiviral drug, was approved by the US Food and Drug Administration (FDA) for the treatment of COVID-19, based on clinical results showing that it shortens time to recovery in adults hospitalized with lower-respiratory-tract infection.[5] Clinical trials investigating the efficacy of convalescent plasma in patients with COVID-19 yielded equivocal results,[6,7] which has recently led the FDA to revise the convalescent plasma emergency use authorization, approving its use only for the treatment of hospitalized patients with COVID-19 early in the disease course or hospitalized patients with impaired humoral immunity. Several single-agent or combined cocktail SARS-COV-2–specific monoclonal antibodies (mAbs) were authorized for use in nonhospitalized patients with mild to moderate COVID-19. It is unclear whether these antibodies were used in the present study population and whether that may have contributed to the better outcome in the late cohort.

Although the authors did not provide data regarding the specific anti–COVID-19 agents used in each cohort,[1] the findings that the mortality rate has dropped

in hospitalized patients, including in those requiring supplemental oxygen, but not in those requiring ICU level care, may reflect better management of patients over time, but also highlight the significance of early introduction of various anti–COVID-19 therapies to prevent clinical deterioration to ICU level care. The findings that corticosteroids increased both secondary infections and death rates in patients with CLL and COVID-19 are intriguing. In the RECOVERY trial,[8] the use of dexamethasone improved survival in patients hospitalized with COVID-19 who received respiratory support. Perhaps the impaired immune reactions in patients with CLL moderate the hyperinflammatory reactions to COVID-19, thus turning corticosteroids beneficial effects to somewhat redundant in this frail population.

After the acute phase of SARS-CoV-2 infection, seroconversion is noted in nearly all immunocompetent subjects, whereas it was documented in only 60% of the patients with CLL.[1] Failure to produce protective antibodies may put seronegative patients at risk for reinfection with SARS-CoV-2 and consequently justifies vaccinating all patients with CLL who have recovered from COVID-19. Likewise, patients with CLL may develop persistent COVID-19 infection, as result of their inability to effectively eradicate the virus. In such cases, prolonged shedding of infectious SARS-CoV-2 virus and within-host genomic evolution may eventually lead to emergence of new virus variants.[9] Antibody-mediated response to COVID-19 vaccines in patients with CLL is also impaired and impacted by disease activity and anti-CLL treatment.[10] High rates of humoral responses to COVID-19 vaccine were observed in patients with CLL in remission after treatment. Treatment-naive patients had a lower rate of response to vaccination, whereas only a minority of patients on active treatment at the time of vaccination responded.[10] Recently, administration of a third messenger RNA COVID-19 vaccine dose to solid-organ transplant recipients was shown to significantly improve humoral response to the vaccine, as 44% of seronegative patients became seropositive after a third dose.[11] Given the high risk of severe COVID-19 disease and impaired antibody-mediated immune response to the SARS-CoV-2 virus and its vaccine in patients with CLL, a booster dose may be justified in patients with CLL who fail to achieve seropositivity after 2 vaccine doses.

In summary, Roeker et al report on the recent outcome of patients with CLL and COVID-19, showing decreased risk of death, and provide hints regarding the efficacy of specific treatments in these patients. The gathering data call for early application of antiviral drugs, mAbs, and convalescent plasma as well as improved vaccination strategy, to improve the odds for patients with CLL confronting COVID-19. As the global COVID-19 pandemic is ongoing and seems far from resolution, especially as the virus continues to mutate, well-designed, large-scale prospective studies, on the clinical course, outcomes, the efficacy of specific therapeutics, and vaccination timing and schedule, in patients with CLL and COVID-19, are still warranted.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

REFERENCES

1. Roeker LE, Eyre TA, Thompson MC, et al. COVID-19 in patients with CLL: improved survival outcomes and update on management strategies. *Blood.* 2021;138(18):1768-1773.
2. Forconi F, Moss P. Perturbation of the normal immune system in patients with CLL. *Blood.* 2015;126(5):573-581.
3. Scarfò L, Chatzikonstantinou T, Rigolin GM, et al. COVID-19 severity and mortality in patients with chronic lymphocytic leukemia: a joint study by ERIC, the European Research Initiative on CLL, and CLL Campus. *Leukemia.* 2020;34(9):2354-2363.
4. Vijenthira A, Gong I, Fox TA, et al. Outcomes of adult and pediatric patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 1847 patients [published online ahead of print 17 December 2020]. *Blood.* doi:10.1182/blood.2020008824.
5. Beigel JH, Tomashek KM, Dodd LE, et al; ACTT-1 Study Group Members. Remdesivir for the treatment of Covid-19 - final report. *N Engl J Med.* 2020;383(19):1813-1826.
6. Simonovich VA, Burgos Pratx LD, Scibona P, et al; PlasmAr Study Group. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. *N Engl J Med.* 2021; 384(7):619-629.
7. Libster R, Pérez Marc G, Wappner D, et al; Fundación INFANT–COVID-19 Group. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. *N Engl J Med.* 2021;384(7):610-618.
8. Horby P, Lim WS, Emberson JR, et al; RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med.* 2021;384(8): 693-704.
9. Avanzato VA, Matson MJ, Seifert SN, et al. Case study: prolonged infectious SARS-CoV-2 shedding from an asymptomatic immunocompromised individual with cancer. *Cell.* 2020;183(7):1901-1912.e9.
10. Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. *Blood.* 2021;137(23):3165-3173.
11. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients [published online ahead of print 23 June 2021]. *N Engl J Med.* 2021;NEJMc2108861.

DOI 10.1182/blood.2021013286

MYELOID NEOPLASIA

Comment on Astolfi et al, page 1773

A viral cause of APL

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In this issue of *Blood*, Astolfi et al report the first known cases of acute promyelocytic leukemia (APL) caused by integration of the ubiquitous, seemingly nonpathogenic torque teno mini virus (TTMV) into the *RARA* locus.[1]

APL accounts for 5% to 10% of pediatric and adult acute myeloid leukemia (AML) and is characterized by specific clinical and biologic features and is managed by a unique therapeutic approach. Indeed, compared with other AML subtypes, it seems APL diagnosis, biology, and therapy are well defined with little left to be worked out. The diagnosis and management of APL often proceeds down a relatively predictable path beginning with the patient presenting with a variably high white blood cell count with promyelocytic blasts, typically with characteristic intense azurophilic granules and obvious Auer rods. Diagnosis is facilitated by the