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blood® commentary

CLINICAL TRIALS AND OBSERVATIONS

Comment on Niemann et al, page 445

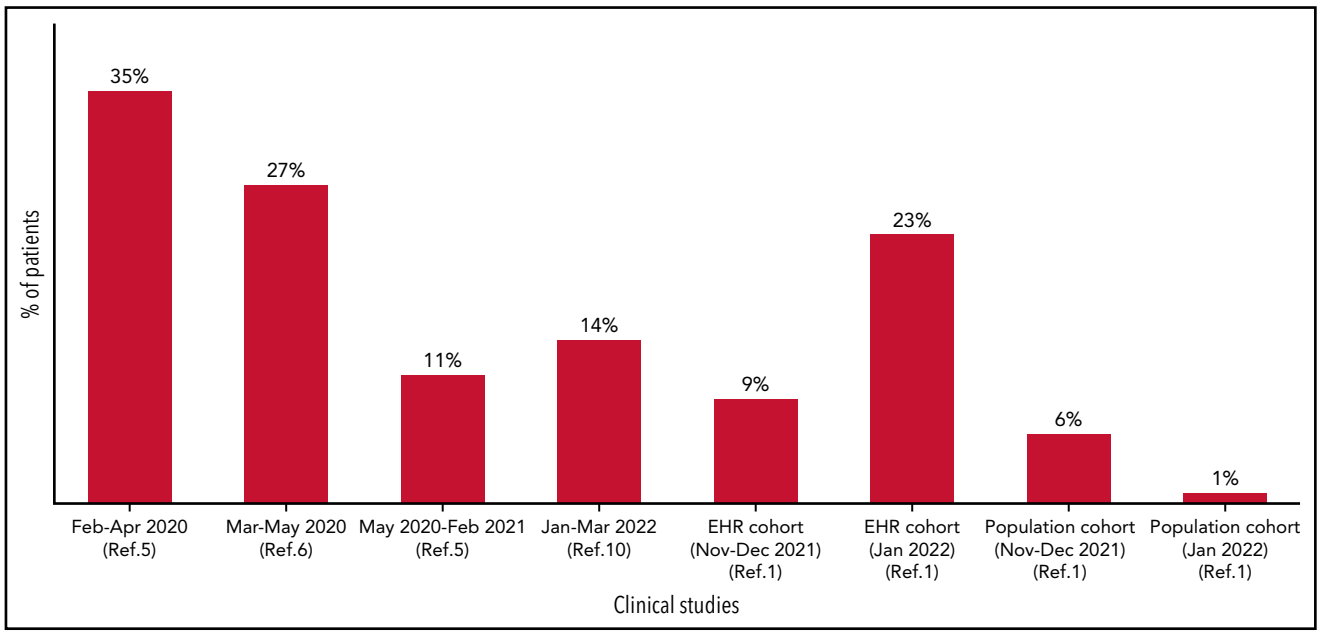
CLL and COVID-19: light at the end of the tunnel?

Lydia Scarfò[1] and Yair Herishanu[2] | [1]Università Vita Salute San Raffaele; [2]Tel Aviv Sourasky Medical Center

In this issue of *Blood*, Niemann et al[1] investigate the outcomes of coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in patients with chronic lymphocytic leukemia (CLL). The outcomes cover a span of almost 2 years. The authors focused on the surges of different SARS-CoV-2 variants, and they found a much milder course for COVID-19 during the time that the omicron variant was dominant, with a 30-day mortality rate as low as 1% in younger patients not tested at hospital sites.

On the basis of the data collected in the Danish registry, the authors analyzed the outcomes of populations tested at hospital sites (patient data were thereby included in the electronic health records [EHRs] system) during 4 different time periods between March 2020 and the end of January 2022. They found a significant improvement in the period from November 2021 to January 2022, when omicron and its subvariant BA.2 first emerged and then became dominant. The 30-day hospital admission rates declined from 83% to 55%, intensive care unit (ICU) admission rates declined from 13% to 0%, and 30-day overall survival improved from 83% to 91% (during the period when the omicron variant dominated), but decreased again to 77% with the occurrence of the BA.2 subvariant. Even more importantly, when the analysis was extended to include 640 patients in the CLL registry who tested positive (by polymerase chain reaction assay) for SARS-CoV-2 outside the EHRs system, the 30-day overall survival increased from 88% to 98% over the observation period.

With more than 510 000 000 infections and more than 6 200 000 cumulative deaths worldwide (https://covid19.who.int/ as of 15 May 2022), COVID-19 has had a dramatic impact on populations all over the world. Patients with hematologic malignancies are more profoundly affected because they have a 34% mortality



COVID-19–related mortality in patients with CLL over time. The COVID-19–related mortality in patients with CLL during different waves of COVID-19 (initial studies on the left) is depicted. Initial studies (up to 35%, on the left) reported the highest mortality rate for COVID-19, whereas more recent retrospective series documented a much lower mortality rate (1%-23%, depending on the setting of data collection).

rate when hospitalized as a result of COVID-19.[2] Among those with hematologic malignancies, patients with CLL were at higher risk because of CLL-associated immune dysfunction. Patients with CLL who required active treatment had a worse outcome, even in the era of targeted agents. Large retrospective series during the first wave of COVID-19 documented a case fatality rate as high as 33%,[3,4] with an improvement to 20% during the second wave in 1 international retrospective cohort of hospitalized patients with CLL.[5] However, this more favorable outcome was not confirmed in a large European cohort of 941 patients with CLL and COVID-19 (see Figure); in that case, the fatality rate of hospitalized patients actually increased slightly to 38.4%.[6]

Since December 2020, the availability of vaccines against SARS-CoV-2 raised hopes of preventing severe disease. As expected, vaccine response is impaired in patients with CLL. Only 40% of patients developed detectable antibodies after 2 vaccine doses (ranging from 80% in those in clinical remission to 0% in those receiving active anti-CD20 therapy) with generally lower titers in those who do respond.[7] The jury is still out regarding the dynamics of the T-cell response after vaccination. The results are contradictory regarding the generation and reactivity of $CD4^+$ and $CD8^+$ T cells against SARS-CoV-2 in patients with hematologic malignancies.[8] This is expected, considering that the evaluation of T-cell function is complex and that it is more difficult to reliably assess cellular responses. Despite the need for further studies to better address the immune response, primary vaccination and booster doses are recommended for all patients with CLL regardless of serological results. In addition to vaccines, several treatment modalities, including monoclonal antibodies (eg, sotrovimab, etesevimab-bamlanivimab, imdevimab-casirivimab) and antiviral treatments (initially remdesivir, then nirmatrelvir-ritonavir and molnupiravir) have been approved to prevent infections from progressing from mild-moderate to severe. These treatments have been administered to immunocompromised patients and are associated with improved outcomes.[8] However, most of the monoclonal antibody products rapidly fell from grace because they were largely ineffective for the novel variants of concern that keep emerging. Recently, the combination of 2 long-acting antibodies, tixagevimab and cilgavimab, has been authorized as pre-exposure prophylaxis for COVID-19 in patients who are moderately to severely immunocompromised. The initial authorized dose of tixagevimab/cilgavimab was increased to 300 mg/300 mg because higher doses increase the chance of preventing infection by the omicron subvariants.

In this challenging scenario, the study by Niemann et al suggests that the odds that patients with CLL can control their SARS-CoV-2 infection and avoid severe manifestations (including death) are improving. Recent work has suggested that, in the general population, the risk of severe outcomes after SARS-CoV-2 infection is substantially lower for those infected with the omicron variant, including for more severe end points.[9] The analysis by Niemann et al concentrates on immunocompromised patients and confirms that this reduction in the risk of severe outcomes also holds true for younger patients with CLL who are not included in the EHR system. When focusing on the cohort with data extracted from the EHRs system, even though hospitalization and ICU admission rates declined, the mortality rate maintained high at 23% during the period when omicron sublineage BA.2 dominated. Because the EHR population was characterized by an older median age and the need for hospital access, this category of patients is more fragile. They would benefit from timely screening, prompt intervention, and close follow-up to avoid a dismal outcome. These findings are in keeping with the recent report from the Israeli group[10] of a 31% case fatality rate in hospitalized patients with CLL during the time of omicron dominance (January to March 2022).

The study by Niemann et al has some limitations. The data we analyzed were extracted from EHRs and/or a registry in which information on SARS-CoV-2 antibody levels, number of vaccine doses received, and specifics of COVID-19 prophylaxis were missing. No information on hospitalization rate or ICU admission was available for the population cohort. Nevertheless, the findings of this study, if validated in different settings, would suggest that we are indeed making progress in managing patients with CLL and COVID-19. Although it is not clear how much each of the pieces (vaccines, other prophylactic and mitigation measures, treatment, and the properties of viral strains) contributed to the improvement, the trend is favorable. Hopefully, we can continue to drastically reduce the mortality rate in this vulnerable patient population by maximally exploiting each component of the antiviral strategies and improving them. It is also critically important to make each of these components available to all patients with CLL worldwide. Progress has been made, but more needs to be done to remove the COVID-19 shackles from patients with CLL.

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GENE THERAPY

Comment on Shalabi et al, page 451

Reverse translational studies inform dual-targeted CAR T-cell design

Rayne H. Rouce and Lauren Scherer | Baylor College of Medicine

In this issue of *Blood*, Shalabi et al[1] report on the safety, efficacy, and clinical limitations of a novel bivalent MSCV-CD19/CD22-4-1BB (CD19.22.BBζ) chimeric antigen receptor (CAR) T-cell in heavily pretreated patients with B-cell acute lymphoblastic leukemia, including those previously treated with CD19- or CD22-directed CAR T cells.

This report is timely, given the high remission rates after treatment with CAR T cells that target dual B-cell antigens, which has enabled consolidative stem cell transplantation and disease-free survival in some patients.[2-5] Furthermore, as the use of (and indications for) commercial and investigational CAR T cells targeting CD19 or CD22 increases, the number of patients seeking treatment with a dual-targeted CAR T-cell product after previous CAR T-cell therapy has also increased. Treating patients who previously received CAR T cells with a subsequent autologous CAR T-cell therapy broaches new unanswered questions, which the authors begin to address in their article.

In their phase 1 trial, Shalabi et al found that CD19.22.BBζ CAR T cells were well-tolerated and effective, with 12 of 20 patients achieving complete responses and an additional 4 patients clearing marrow disease, albeit with residual extramedullary disease. Compared with patients in similar trials, a larger proportion of patients in their trial (40%) had evidence of extramedullary disease at enrollment. This highlights the refractory nature of the disease and raises questions regarding the trafficking of CAR T cells to extramedullary sites such as the central nervous system along with efficacy at these sanctuary sites.[6] In addition, 30% of patients in their study had received previous CAR T-cell therapy.

Multi-antigen–targeting CARs are believed to reduce antigen modulation and thus offset the risk of antigen escape, a phenomenon observed after therapy with CARs that target a single antigen.[7,8] However, the best strategy for developing dual-targeting CARs has not yet been established. The use of a bivalent vector (tandem or bicistronic) allows for uniform expression of both targeting moieties (single chain variable fragments [scFv's]) and the relative ease of manufacturing compared with co-transduction or co-infusion.[9] Designing a bivalent CAR requires complex vectors consisting of variable regions that influence the expansion, function, and persistence of the final product. Furthermore, the promoter region of the CAR vector has an impact on T-cell properties, including transgene expression, transduction, surface density, and function.[10]

Shalabi et al identified some limitations of their construct after infusion, noting decreased expansion and persistence compared with the previously studied human elongation factor 1α (EF1α)-CD22.BBζ CAR. In a series of experiments, they further probed the mechanisms responsible for these observations. The authors hypothesized that the decreased expansion and persistence of their murine stem cell virus (MSCV) bivalent CAR was a result of the difference in promoter region because the CAR was otherwise comparable to their EF1α-CD22.BBζ CAR. In an NALM-6 NSG (NOD.Cg-*Prkdcscid*Il2rgtm1Wjl/SzJ [The Jackson Laboratory]) mouse model, the authors found that CD19.22BBζ CAR–expressing $CD8^+$ T cells incorporating either the MSCV or EF1α promoter region demonstrated an exhausted phenotype. Although pretreatment antigen density did not correlate with response (as in previous reports regarding CD19/CD22 CAR T cells[2,3]), CD19.22BBζ CAR T cells containing either promoter had attenuated responses to CD22 compared with CD22.BBζ CAR T cells. Previous studies reported that diminished responses to CD22 can limit in vivo expansion and functionality of other dual-targeting products,[2] which underscores the importance of efforts to enhance CD22 targeting in dual-targeting CAR T cells. Suboptimal CD22 scFv activity seems to limit the functionality of the CD19 component as well.

Limited persistence has been reported in other clinical trials of dual-targeted CD19/CD22 CAR T cells,[2-5] and a variety of factors influence attenuated expansion and persistence. These factors include the design of the CAR, limited binding of the CAR with its cognate antigen (as reported by Shalabi et al), reduced CAR signaling, and exhausted T-cell phenotype correlating with abrogated function.[11] In the AUTO3 study (United Kingdom), the authors found that enhanced persistence was associated with a higher proportion of CD4- or CD8-naïve cells within the CAR product, regardless of treatment dose, and low programmed cell death protein 1 (PD1) expression at peak expansion.[2]

In the setting of reduced persistence, especially in patients who received a previous CAR T-cell product, immunological rejection of CAR T cells must be considered because scFv's are often derived from mice. Although there was no apparent correlation between response and the presence of human anti-mouse antibodies (HAMAs) in the Shalabi et al study, measurements of HAMAs were limited to the first month. Assessment of HAMAs and evidence of T-cell–mediated rejection at later timepoints will be key in dissecting the impact of each of these factors on CAR T-cell function. Future