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CLINICAL TRIALS AND OBSERVATIONS

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COVID-19 and blood cancer in the vaccination era

Lisa K. Hicks[1,2] and Abi Vijenthira[2,3] | [1]St. Michael's Hospital; [2]The University of Toronto; and [3]Princess Margaret Cancer Centre

In this issue of *Blood*, Pagano et al report on the outcomes of over 1500 patients with blood cancer and breakthrough COVID-19 reported to the EPICOVIDEHA (Epidemiology of COVID-19 Infection in Patients with Hematological Malignancies: European Haematology Association) registry.[1] Their report is unique for its size, detail, and contemporary relevance, as Omicron infections make up a majority of genotyped cases in their sample.

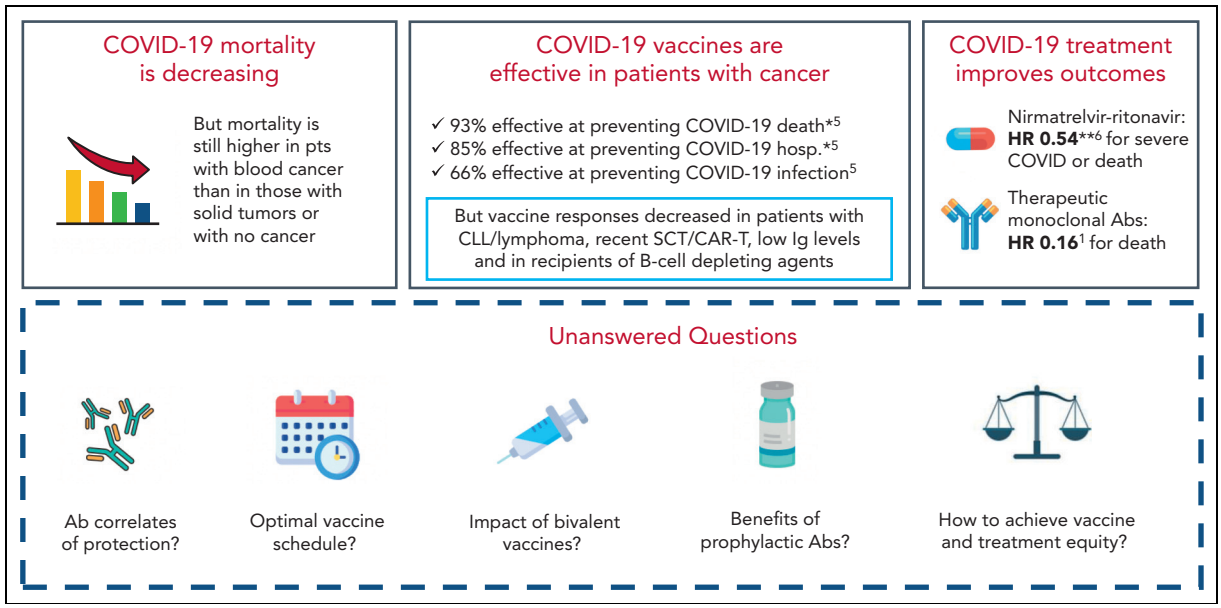
Patients with hematologic malignancy are uniquely vulnerable to infection, owing to both immune dysfunction associated with their cancer and the treatments they receive. Since the early days of the pandemic, increased COVID-19 morbidity and mortality were anticipated in this population and now have been widely reported.[2,3] Less clear is the extent to which this vulnerable population benefits from COVID-19 vaccination and treatment. Pagano et al shed light on these critical questions.

The authors report an overall mortality rate of 9.2% among patients with blood cancer and breakthrough COVID-19, a marked improvement compared to the 31.2% mortality rate observed by the same registry earlier in the pandemic. Improvements in severe or critical COVID-19 (42.7% vs 63.8%), hospitalization (53.2% vs 73%), and intensive care unit admission (9.8% vs 18.1%) are also reported. The outcomes in the Pagano et al paper are consistent with other reports of decreasing COVID-19 mortality over time, a phenomenon that predated COVID-19 vaccines but appears to have accelerated following widespread vaccination.[2,4]

Recent reports suggest that one of the most important COVID-19 protections available to patients with cancer is vaccination. Using a population-based administrative dataset from the United Kingdom, Lee et al estimate that among patients with cancer, 2 doses of COVID-19 vaccine are 66% effective at preventing COVID-19 infection, 85% effective at preventing COVID-19 hospitalization, and 93% effective at preventing COVID-19 death (see figure).[5] The article by Lee et al predates the Omicron era, but similar findings were reported in a large study of high-risk patients from Israel (including patients diagnosed with cancer in the previous year) when the Omicron variant was the dominant strain.[5] Researchers found that adequate vaccination is associated with a significantly lower risk of severe COVID-19 and/or death (adjusted hazard ratio 0.20, 95% confidence interval 0.17-0.22).[6]

The Pagano study provides important insights into patient, disease, and treatment factors associated with worse breakthrough COVID-19 outcomes. Using a multivariable analysis, they report that advanced age, the presence of 2 to 3 comorbidities, and having active cancer are all associated with increased mortality in the 30 days following COVID-19 breakthrough infection. These variables have been associated with worse COVID-19 outcomes in previous reports.[3] Interesting to note is that Pagano et al did not find a significant association between the number of vaccine doses and COVID-19 mortality. This result is unexpected, as receiving 3 doses of COVID-19 vaccine is associated with decreased COVID-19 morbidity and mortality in other settings,[7] and with increases in neutralizing antibody levels in patients with hematologic malignancy.[8] Moreover, serologic responses and vaccine effectiveness have been observed to wane in older patients and those with cancer,[5] an effect that potentially can be reversed with booster doses.[8] One possibility is that the Pagano et al study was underpowered to detect this association; alternatively, even 3 or more vaccine doses may be insufficient protection for some patients with blood cancer. Emerging data suggest that some patients with hematologic malignancy, such as those with chronic lymphocytic leukemia or lymphoma, those with hypogammaglobulinemia, recent recipients of cellular therapy, and those receiving B cell–depleting therapies do not mount effective serologic responses to vaccination.[4,8] The cohort in the study by Pagano et al was enriched with patients with lymphoid malignancies, a predominance that may reflect a higher rate of breakthrough infection in this population, and introduces the possibility that reduced vaccine response in this subgroup could have diluted a relationship between vaccine boosters and mortality in the whole cohort.

A final important finding of Pagano et al is that treatment with antispike antigen monoclonal antibodies, alone or in



COVID-19 in patients with blood cancer: a snapshot. *In post hoc analysis. **Among high-risk patients. Ab, antibody; CAR-T, chimeric antibody T-cell therapy; CLL, chronic lymphocytic leukemia; hosp, hospitalization; HR, hazard ratio; Ig, immunoglobulin; pts, patients; SCT, stem cell transplant.

combination with antivirals, is associated with decreased mortality. Their findings align with 2 recent, real-world studies reporting improved COVID-19 outcomes with sotrovimab in the general population pre-Omicron, and with ritonavir-boosted nirmatrelvir (nirmatrelvir-ritonavir) in high-risk patients during the Omicron era.[6,9] Pagano et al do not report the specific monoclonal antibodies used in their study, and readers are cautioned that some COVID-19 monoclonal antibodies are ineffective against the Omicron variants that are currently dominant.[10] Nonetheless, the findings offer some reassurance for patients with blood cancer, who may not be protected by vaccination, and support the prioritization of patients with hematologic malignancies for COVID-19 treatment.

The study by Pagano et al has important limitations. Like all registry studies, theirs is vulnerable to selection bias and nonrandom, regional variations in both practice and patient behavior. A recent report on COVID-19 and chronic lymphocytic leukemia observed that patients identified via review of hospital records tended to be older and to have markedly worse outcomes than those identified via population-level data, suggesting a selection bias toward inclusion of sicker patients with use of hospital-based data.[2] As well, the study by Pagano et al is uncontrolled and makes comparisons to historical, pre-vaccination data. Caution should be exercised in making such comparisons, as the datasets may differ in multiple ways.

Observational data are helpful for deepening our understanding of outcomes in patients with diverse ages, ethnicities, comorbidities, and exposures. However, teasing apart the differential impact of dynamic factors, such as vaccination rates, patient behaviors, and COVID-19 virulence can be difficult, or even impossible. To determine the true impact of COVID-19 interventions, we need randomized controlled trials that include patients with blood cancer. Future research will determine optimal vaccine schedules, the serologic correlates of protection, the impact of both bivalent vaccines and prophylactic monoclonal antibodies, and strategies to ensure equitable provision of COVID-19 vaccines and treatments (see figure). We need some of that research to include patients with hematologic malignancy.

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Wang et al, page 2788

Restoring NK cell functions in AML relapse

Sena Kim and Jaebok Choi | Washington University School of Medicine

In this issue of *Blood*, Wang et al[1] demonstrate that glycoprotein A repetitions predominant (GARP)–mediated activation of TGF-β1 by regulatory T cells (Tregs) downregulates the effector functions of natural killer (NK) cells in the bone marrow of patients with acute myeloid leukemia (AML) with early relapse after allogeneic hematopoietic cell transplantation (allo-HCT), and that pharmacologic blockade of TGF-β1 signaling using galunisertib or anti-TGF-β1 antibodies can restore the killer instinct of human NK cells.

Disease relapse remains the main cause of death after allo-HCT for AML.[2,3] Although donor lymphocyte infusion (DLI; primarily T cells) has been used to treat AML relapse, the survival benefit for patients with relapsed AML by DLI is far from satisfactory with a 2-year overall survival (OS) of 25% and a 5-year OS of 15%.[4] In addition, DLI is associated with a risk of graft-versus-host disease (GVHD), a leading cause of non-relapse mortality after DLI or allo-HCT.[3,4] Thus, finding a means to prevent and treat AML relapse without inducing GVHD is an unmet medical need.

The current study proposes that the restoration of NK cell functions by targeting TGF-β1 may control disease relapse. NK cells are the first lymphocytes to reconstitute after allo-HCT and their successful recovery is associated with protection against AML relapse.[5] In contrast to T cells, NK cells play a regulatory role in GVHD in addition to their potent anti-leukemia effect in the allogeneic setting.[6] Thus, a number of NK cell–based immunotherapies have been investigated including a phase I clinical trial with donor memory-like NK cells for patients with relapsed AML after allo-HCT.[7,8] Nonetheless, NK cell immunotherapies have been disappointing likely owing to impairment of NK cell cytotoxicity, thereby allowing AML cells to escape from immunologic destruction. In addition, the killer activity of NK cells derived from the donor graft against host AML has not been definitively demonstrated in relapsed AML after allo-HCT. Do NK cells, reconstituted after allo-HCT, manifest an active anti-leukemia effect? What causes NK cell dysfunction after allo-HCT? Can we develop therapeutic strategies to restore the cytotoxicity of NK cells against relapsed AML? If so, we may limit the need for expensive and labor-intensive ex vivo cellular manipulations involved in NK cell–based immunotherapies for hematologic malignancies and even for solid tumors (eg, adoptive transfer of autologous or allogeneic NK cells, memory-like NK cells, CAR NK cells, etc).

The study by Wang et al identifies the GARP-TGF-β1 pathway between Tregs and NK cells in the bone marrow of patients with AML as the major player in the loss of NK cell cytotoxicity against AML. The authors first showed that the levels of active TGF-β1 were significantly increased in the bone marrow of patients with relapsed AML than those without relapse even though the total amounts of TGF-β1 (both latent and active) in the bone marrow were comparable between the 2 groups. These findings lead them to the question of whether or not the increased levels of active TGF-β1 disarmed NK cells in the bone marrow (BMNK cells). They found that active TGF-β1 impaired the effector functions of BMNK cells by reducing the expression of IFN-γ, TNF-α, CD107a, GZMB, NKp30, and NKG2D and suppressing mTOR activity and mitochondrial respiration (OXPHOS) (see figure). Next, the authors determined the role of GARP that has been known to activate latent TGF-β1 in the context of AML. GARP + CD4 + T cells (FOXP3 + Tregs) were significantly more abundant in the bone marrow of patients with relapse than those without relapse. In addition, cytotoxicity of BMNK cells was significantly reduced when BMNK cells were pretreated with latent TGF-β1 in the presence of GARP + CD4 + T cells. Consistent with this, BMNK cells purified from patients with AML with relapse had significantly lower anti-tumor activities than those from patients without relapse. Importantly, the authors demonstrated that TGF-β1 inhibitors, such as galunisertib and anti-TGF-β1 antibodies, could restore the anti-leukemia effector functions of BMNK cells. Thus, the current study by Wang et al urges us to pay attention to the GARP-TGF-β1 pathway as a potential therapeutic target to prevent and treat AML relapse, thereby improving the survival of patients after allo-HCT or NK cell–based immunotherapies.

It is, nonetheless, also important to acknowledge that there are a few gaps that need to be further studied. Their previous report suggests that FBP1 is a key component in TGF-β1 signaling–mediated NK cell dysfunction in lung cancer.[9] Does FBP-1–induced inhibition of glycolysis also play a role in AML relapse? Can FBP-1 inhibitors effectively control AML relapse by restoring NK cell function after allo-HCT? Because TGF-β1 signaling suppresses alloreactive T cells as well, it would be important to examine the status of allogeneic T cells in the bone marrow of patients with relapsed AML. Because TGF-β1 contributes to Treg differentiation and