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risk-mitigation strategies for cytokine release syndrome management with pre-emptive tocilizumab can be considered without changes in CAR-T cell efficacy and improves the toxicity profile.[8,9] Earlier admission to intensive care in patients at high-risk of cytokine release syndrome might also improve outcomes, as seen in previous studies in haematological malignancies, and might paradoxically reduce the duration of stay in intensive care.[10]

In conclusion, despite the limitations of Azoulay and colleagues' study due to its partly retrospective nature and absence of available follow-up data regarding treatment responses, this large, multicentre study provides a real-world view of CAR T-cell management in intensive care units and how this is implemented across both commercial and research CAR T-cell products in patients with various haematological malignancies. As the CAR T-cell field continues to expand, the lessons learned from these early experiences will be crucial in informing outcomes with the next generation of CAR T-cell constructs for which toxicities might further vary. Overall, prevention is the best cure, and approaches to mitigate the severity of cytokine release syndrome and ICANS and lessen the need for intensive care are needed to improve overall outcomes.

We declare no competing interests.

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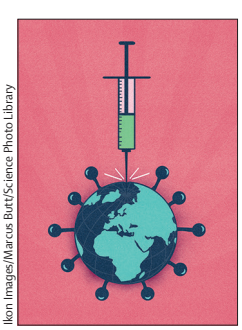
1 Maus MV, Alexander S, Bishop MR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events. *J Immunother Cancer* 2020; **8:** e001511.
2 Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. *Blood* 2016; **127:** 3321–30.
3 Gutierrez C, McEvoy C, Mead E, et al. Management of the critically ill adult chimeric antigen receptor-T cell therapy patient: a critical care perspective. *Crit Care Med* 2018; **46:** 1402–10.
4 Azoulay E, Shimabukuro-Vornhagen A, Darmon M, von Bergwelt-Baildon M. Critical care management of chimeric antigen receptor T cell-related toxicity. Be aware and prepared. *Am J Respir Crit Care Med* 2019; **200:** 20–23.
5 Azoulay E, Castro P, Maamar A, et al. Outcomes in patients treated with chimeric antigen receptor T-cell therapy who were admitted to intensive care (CARTTAS): an international, multicentre, observational cohort study. *Lancet Haematol* 2021; **8:** e355–64.
6 Hill JA, Li D, Hay KA, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. *Blood* 2018; **131:** 121–30.
7 Park JH, Romero FA, Taur Y, et al. Cytokine release syndrome grade as a predictive marker for infections in patients with relapsed or refractory B-cell acute lymphoblastic leukemia treated with chimeric antigen receptor T cells. *Clin Infect Dis* 2018; **67:** 533–40.
8 Kadauke S, Myers RM, Li Y, et al. Risk-adapted preemptive tocilizumab to prevent severe cytokine release syndrome after CTL019 for pediatric B-cell acute lymphoblastic leukemia: a prospective clinical trial. *J Clin Oncol* 2021; **39:** 920–30.
9 Gardner RA, Ceppi F, Rivers J, et al. Preemptive mitigation of CD19 CAR T-cell cytokine release syndrome without attenuation of antileukemic efficacy. *Blood* 2019; **134:** 2149–58.
10 Benoit DD, Depuydt PO, Vandewoude KH, et al. Outcome in severely ill patients with hematological malignancies who received intravenous chemotherapy in the intensive care unit. *Intensive Care Med* 2006; **32:** 93–99.

COVID-19 vaccines for patients with haematological conditions



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Patients with haematological conditions have been disproportionately affected by the COVID-19 pandemic. A pooled meta-analysis of 3377 predominantly hospitalised patients with haematological malignancies and COVID-19 reported a mortality rate of 34% (95% CI 28–39). Advanced age (≥60 years) and non-White race were identified as risk factors for death. Mortality rate varied on the basis of the type of malignancy: 53% of patients with acquired bone marrow failure syndromes, 41% of patients with acute leukaemias, 32% of patients with lymphomas, 31% of patients with chronic lymphocytic leukaemia, and 34% of patients with myeloproliferative neoplasms.[1] To place these data in perspective, the mean 30-day rate of mortality or referral to hospice was 11·8% (SD 2·5%) in a cohort study of 38 517 adults admitted to hospital with COVID-19 in the USA.[2] The trajectory of COVID-19 in patients with benign haematological conditions such as haemoglobinopathy, haemophilia, pre-existing arterial or venous thromboembolism, and autoimmune cytopenia is relatively unknown, but as in the general population, is influenced by age and comorbidities.

Authorised COVID-19 vaccines are safe and effective in the general population. Given the high case fatality rate among patients with haematological conditions, prioritisation of COVID-19 vaccines for this group might appear straightforward. However, common to these vaccines is the exclusion of immunocompromised people from landmark phase 3 randomised controlled trials. Relevant exclusion criteria included the use of

immunosuppressive or immunomodulatory agents, immunoglobulin or blood products, asplenia, and autoimmune conditions such as immune thrombocytopenic purpura. Most patients with haematological conditions, therefore, would have been ineligible for these trials. Until COVID-19 vaccines have been rigorously studied in this group, one must examine available data on the immune response to COVID-19 infection and non-COVID-19 vaccines to inform clinical practice and expectations.

Haematological conditions and their treatment are heterogeneous, and so the immune response to infection or vaccination is also expected to be variable. A case series reported 14 (67%) of 21 patients with chronic lymphocytic leukaemia developed IgG antibodies to SARS-CoV-2 nucleocapsid.[3] Those who did not develop antibodies included both treatment-naive patients and patients receiving chronic lymphocytic leukaemia-directed therapy. The seroconversion rate among recipients of haematopoietic stem-cell transplantation and chimeric antigen receptor T-cell therapy was similar at 66% (25 of 38 patients).[4] Intriguingly, B-cell lymphopenia in these patients did not preclude an antibody response to SARS-CoV-2. In acute leukaemia, antibodies against the external spike glycoprotein and internal nucleocapsid were detected in seven (88%) of eight patients.[5] Besides a lower rate of antibody production, the humoral response in patients with haematological conditions is also slower than in the general population. SARS-CoV-2-specific cellular immunity in this group still needs to be characterised.

A 2011 Cochrane review of viral vaccines in patients with haematological malignancies concluded that, despite the low quality of evidence, the possibility of protection outweighed the minor risks of vaccination.[6] Regrettably, there remains a lack of randomised studies to evaluate vaccine efficacy in patients with haematological conditions. One exception is a randomised placebo-controlled trial of adjuvanted recombinant zoster vaccine (RZV) in 569 patients with haematological malignancies.[7] All patients were receiving or had received treatment for their haematological malignancy within 6 months before vaccination. RZV was well tolerated and induced a humoral response in 119 of 148 patients (80% [95% CI 73–86]). This per-protocol analysis excluded patients with non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia, in whom the humoral response rate was between 20% and 50%. Herpes zoster occurred in two patients in the vaccine group who received proximate rituximab therapy. These observations confirm that B-cell depleting therapy, or perhaps B-cell malignancy, weakens the humoral vaccine response and overall vaccine efficacy.

Whether immunisation induces a primary or memory immune response could be an important consideration for specific haematological conditions or treatment. We investigated the de novo humoral immune response to recombinant hepatitis B vaccine and the recall response to RZV in patients with chronic lymphocytic leukaemia.[8] Patients were treatment-naive (32 patients for hepatitis B vaccine and 22 patients for RZV) or receiving a BTK inhibitor for at least 6 months (26 patients for hepatitis B vaccine and 41 patients for RZV). Treatment-naive patients had an impaired humoral response to both vaccines, consistent with previous studies of other immunisations in this population. In patients on BTK inhibitor therapy, hepatitis B surface antibodies were negative in all but one patient at 3 months following vaccination. The rate of seroconversion with RZV was also numerically lower in patients treated with BTK inhibitors (41% [17 of 41]) than treatment-naive patients (59% [13 of 22]) but, in an interim analysis, did not meet statistical significance. It is worth noting that the absence of a humoral response does not inevitably preclude a cellular response to vaccination. Another study of RZV in patients treated with ibrutinib reported a T-cell response in 50% of patients (four of eight) who did not seroconvert.[9] Treatment modification to improve vaccine response is not supported by current evidence, but deserves further study.

On the basis of existing knowledge about immune responses to COVID-19 infection and non-COVID-19 vaccines in patients with haematological conditions, one can anticipate an attenuated response to COVID-19 vaccines in this vulnerable population. Additional measures to mitigate the risk of COVID-19 are available. Household contacts of individuals at high risk of infectious complications have been recommended as a priority group for annual influenza vaccination and, following this logic, should receive COVID-19 vaccines. Passive immunisation via monoclonal antibodies or high-titre convalescent plasma has been shown to reduce viral load and reduce COVID-19 complications.[10]

The prospect of benefit from COVID-19 vaccines must be weighed not only against their general tolerability, but

also the substantial mortality from COVID-19 infection among patients with haematological conditions. Prospective cohort studies will provide information about the immunogenicity of these vaccines. Advocacy to include immunocompromised people in pivotal vaccine trials and an effort to systematically test strategies to boost vaccine response will help protect patients with haematological conditions against COVID-19 and future outbreaks.

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1 Vijenthira A, Gong IY, Fox TA, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood* 2020; **136:** 2881–92.

2 Asch DA, Sheils NE, Islam MN, et al. Variation in US hospital mortality rates for patients admitted with COVID-19 during the first 6 months of the pandemic. *JAMA Intern Med* 2020; published online Dec 22. https://doi:10.1001/jamainternmed.2020.8193

3 Roeker LE, Knorr DA, Pessin MS, et al. Anti-SARS-CoV-2 antibody response in patients with chronic lymphocytic leukemia. *Leukemia* 2020; **34:** 3047–49.

4 Shah GL, DeWolf S, Lee YJ, et al. Favorable outcomes of COVID-19 in recipients of hematopoietic cell transplantation. *J Clin Invest* 2020; **130:** 6656–67.

5 O'Nions J, Muir L, Zheng J, et al. SARS-CoV-2 antibody responses in patients with acute leukaemia. *Leukemia* 2021; **35:** 289–92.

6 Cheuk DK, Chiang AK, Lee TL, Chan GC, Ha SY. Vaccines for prophylaxis of viral infections in patients with hematological malignancies. *Cochrane Database Syst Rev* 2011; **3:** CD006505.

7 Dagnew AF, Ilhan O, Lee WS, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis. *Lancet Infect Dis* 2019; **19:** 988–1000.

8 Pleyer C, Ali MA, Cohen JI, et al. Effect of Bruton tyrosine kinase inhibitor on efficacy of adjuvanted recombinant hepatitis B and zoster vaccines. *Blood* 2021; **137:** 185–9.

9 Zent CS, Brady MT, Delage C, et al. Short term results of vaccination with adjuvanted recombinant varicella zoster glycoprotein E during initial BTK inhibitor therapy for CLL or lymphoplasmacytic lymphoma. *Leukemia* 2020; published online Oct 30. https://doi:10.1038/s41375-020-01074-4

10 Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. *N Engl J Med* 2021; **384:** 229–37.