Dear Editor,

To our knowledge, we report here the first case of CD19 CAR T-cell infusion administered in a 60-year-old male with DLBCL (diagnosed in June 2021, transformed from follicular lymphoma; GCB type, DHS 1 (bcl-2+, c-myc-)) under severe COVID-19 (Omicron/BA.1) associated with acute respiratory distress syndrome (ARDS) requiring invasive mechanical ventilation after lymphodepletion therapy.

The treatment history is shown in Fig. 1a. The decision to proceed with routine CAR T-cell therapy (axicabtagene ciloleucel) was made after the failure of second-line therapy. However, the patient required extended debulking and bridging with polatuzumab vedotin and rituximab (PR) due to a poor performance state caused by heavy tumor load. Leukapheresis was performed after the 5th cycle when clinical improvement and a radiographic partial response had been achieved. After the 6th debulking/bridging therapy course, the patient tested positive for SARS-CoV-2 (Variant B.1.1.529, Omicron BA.1) during routine reverse transcription-polymerase chain reaction (RT-PCR) testing from a nasopharyngeal swab, with no prior vaccination due to personal reasons. As the patient remained asymptomatic and cycle threshold values of repeated SARS-CoV-2 RT-PCRs from nasopharyngeal swabs were >30, standard outpatient lymphodepleting chemotherapy consisting of fludarabine and cyclophosphamide was started on day 29 of the infection. The patient was routinely admitted to the cellular therapy ward for the scheduled CAR T-cell administration (day 34 after first positive SARS-CoV-2 test). Upon admission, the patient reported fever and diarrhea for the last 2 days. Subsequently he developed dyspnea, requiring high-flow nasal oxygen on the day after with dropping RT-PCR CT-value for SARS-CoV-2 down to 18.7. He was immediately transferred to the COVID unit and subsequently to the intensive care unit due to worsening of respiratory symptoms and increasing demand of supplemental oxygen. After non-invasive/continuous positive airway pressure ventilation and one cycle of awake proning, the patient finally required invasive mechanical ventilation with subsequent prone positioning 2 days after initial hospital admission due to severe COVID-19-associated ARDS. The treatment and laboratory parameters of interest during COVID-19 disease are displayed in Fig. 1b. After careful considerations and interdisciplinary discussions involving intensive care, hematology, and cellular therapy specialists to balance the benefits and risks of CAR T-cell administration during severe COVID-19, axicabtagene ciloleucel was infused on the 25th of February 2022. Respiratory function improved during the following days, eventually allowing successful weaning and extubation after 3 days. The patient was transferred to the cellular therapy ward on day 10 and discharged home on day 12 after axicabtagene ciloleucel with complete resolution of respiratory symptoms. No signs of cytokine release syndrome or neurotoxicity occurred during hospitalization and follow-up, CAR T-cell expansion could be demonstrated with flow cytometry on day 11. The 6-month follow-up...
of the patient showed a complete remission on computed tomography with an ECOG performance status of 0.

Optimal timing of lymphodepleting therapy and CAR T-cell administration is critical, even more so during the ongoing COVID-19 pandemic. The EBMT COVID recommendations highlight the intricacies of (asymptomatic) SARS-CoV-2 infection with particular reference to CAR T-cell recipients, in whom a high risk of progression of the
underlying disease must be considered if therapy is deferred [2]. Given the patient’s history of aggressive lymphoma with only partial response to extended debulking/bridging therapy with polatuzumab vedotin and rituximab, proceeding with CAR T-cell therapy was considered an urgent requirement.

In the reported case, we were confronted with the unreported situation of a patient with severe COVID-19 after lymphodepleting chemotherapy for CAR T-cell therapy. After a thorough multidisciplinary discussion, the following considerations led us to proceed with CAR T-cell infusion:

i) The patient had aggressive DLBCL in partial remission, which required continuous treatment for disease control. A treatment-free interval of several weeks, needed by many patients to recover from severe COVID-19 and ICU treatment, was deemed impossible.

ii) Other options for disease control (e.g., PR, tafasitamab, chemotherapy, steroids) were not considered more tolerable than CAR T-cell infusion in the given situation, as the prior lymphodepletion with fludarabine and cyclophosphamide was regarded as the main limitation for infection control and resolution of organ dysfunction. Infusion of the patient’s CD19-CAR T-cells could restore part of the required antiviral T-cell function.

iii) CAR T-cells had already been manufactured and were available for infusion. Postponing the infusion would have required repeating lymphodepletion with the potential risk of COVID-19 re-infection. Furthermore, the patient’s general condition was expected to be impaired after ICU discharge, with the risk of definitive ineligibility for CAR T-cell therapy. Given the disease history, other treatments were not considered promising for inducing long-term remission in our patient.

In general, the COVID-19-related mortality rate in patients with hematologic malignancies remains high and is even more pronounced after stem-cell and CAR T-cell therapies [3]. Optimal timing of transplantation and cell therapy needs to be emphasized even more during this ongoing pandemic. Preventive measures, vaccination, prophylactic and early use of monoclonal antibodies, and antiviral therapies appear to be key factors in the management of immunocompromised patients. Due to the lack of comprehensive and high-quality data on specific subgroups of cancer patients, individualized decisions are often required, underscoring the importance of reporting individual cases, including this case of CAR T-cells in a patient with malignancy during severe COVID-19-associated ARDS. Clinicians and caregivers should be vigilant in enrolling patients in appropriate randomized controlled trials and international (open) registries to provide higher-quality evidence for specific subgroups of COVID-19 patients [3, 4].

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Data availability For data sharing, please contact the corresponding author (philipp.staber@meduniwien.ac.at).

Declarations

Ethics The patient gave written informed consent for publication of his case.

Conflict of interest The authors declare no competing interests.

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