

MINI-REVIEW

How to manage chimeric antigen receptor T cell recipients upon encountering COVID-19 infection?

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Abstract

Chimeric antigen receptor (CAR) T cell recipients are considered at higher risk of SARS-CoV-2 infection, more severe COVID-19 illness, and poorer outcomes compared to the general population due to their impaired humoral immunity. Managing COVID-19 in these vulnerable patients is particularly challenging. In this review, we provide a brief overview of the characteristics of COVID-19 infection in CAR-T cell recipients, including the pre-treatment assessments and the timing for initiating CAR-T cell therapy, the treatment of COVID-19 during CAR-T cell therapy, and considerations for SARS-CoV-2 vaccination. Our aim is to offer practical strategies to help clinicians conduct safer and more effective CAR-T cell therapies in the post-COVID-19 pandemic era. The therapeutic approach to COVID-19 in this patient population must be individualized. In regions affected by the SARS-CoV-2 outbreak, CAR-T cell therapy is recommended to be conducted at well-established medical centers with expertise in CAR-T. This approach ensures optimal, comprehensive care throughout the treatment process, with the involvement of a multidisciplinary team being essential to the patient's care.

Keywords: SARS-CoV-2; COVID-19; CAR-T; Hematological malignancies; Treatment; Vaccine

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1. Introduction

In the post-COVID-19 pandemic era, viral infections have become highly prevalent, leading to vulnerable individuals contracting the virus up to 3 – 4 times/year in some countries.¹ Patients with hematological malignancies (HM) receiving chimeric antigen receptor (CAR) T cell therapy are much more susceptible to SARS-CoV-2 infection due to the negative influence of their primary diseases and prior treatments, especially CAR-T cell therapy itself, which lead to ongoing B-cell aplasia, T-cell depletion, hypogammaglobulinemia, and cytopenia. This severe immunodeficiency places them

at an elevated risk for severe or critical disease and adverse outcomes following SARS-CoV-2 infection, with studies reporting a COVID-19-attributable mortality rate of up to 41%, which is significantly higher than that observed in the general population. Thus, managing this vulnerable population is extremely challenging.

Zhang *et al.*² published the recommendations for managing CAR-T cell recipients in the post-COVID-19 pandemic era. This study was conducted by a multidisciplinary and interprofessional team based at the National Regional Medical Center. It provides invaluable clinical experience gained from the management of CAR-T cell recipients during the COVID-19 pandemic over the past 4 years. Given that immunocompromised people are usually not prioritized for inclusion in clinical studies, such as vaccine trials and prospective cohort studies, decision-making algorithms based on consensus are extremely important. In addition, other cell-based immunotherapies, such as CAR natural killer-cell (CAR-NK) and T-cell receptor-engineered T-cell (TCR-T), can benefit from the clinical experience gained from this research.³ This work can serve as a template for clinicians to manage other potential pandemics similar to COVID-19 in the future.

2. Characteristics of COVID-19 infection in CAR-T cell recipients

CAR-T cell recipients constitute a distinct and vulnerable demographic in the context of COVID-19, with their immune status intricately influenced by a multitude of factors, including age, comorbidities, the type and stage of their primary HM, and prior treatments. Typically, these patients have undergone multiple lines of chemotherapy, including anti-CD20 therapies.⁴ A retrospective analysis has identified several risk factors associated with an increased likelihood of developing severe COVID-19 infection. These factors include being over 60 years of age, having non-lymphoma tumors, chronic kidney disease, chronic obstructive pulmonary disease, a body mass index of 30 or higher, severe heart disease, and diabetes.⁵ Furthermore, the immune status of the patients is significantly impacted by the phenotype, composition, and dosage of the CAR-T cells. Notably, the highest mortality rates have been observed in patients with acute myeloid leukemia.⁶ Patients treated with B-cell maturation antigen-CAR-T have been noted to experience pronounced immunoglobulin deficiency.⁷ The immune status of CAR-T cell recipients is pivotal to their treatment response and outcomes in COVID-19, particularly in severe or critical cases. A dynamic assessment of immune status, encompassing absolute lymphocyte and B-cell

counts along with their functionality, is of paramount importance.^{8,9}

CAR-T cell recipients infected with COVID-19 not only increase their susceptibility to the virus but also hamper their ability to mount an effective defense against it. They often experience a longer duration of severe symptoms, which necessitates prolonged hospital stays. The median duration of hospitalization for this cohort has been reported as 25 days, with some patients require up to 171 days.² Furthermore, nearly half of these patients required admission to the ICU with a median duration of 14 days.²

Due to their compromised immunity, CAR-T cell recipients usually have prolonged viral clearance, with a mean of 61 days, which is significantly longer than in immunocompetent individuals.^{10,11} This extended viral presence not only complicates the treatment and recovery process but also poses a potential risk for the emergence of new viral variants.¹² The dominant hypothesis based on the emergence of Omicron suggests it evolved in an immunocompromised patient with a chronic COVID-19 infection.¹³ Another hypothesis suggests it developed in regions where viral sequencing is absent or uncommon.¹³ Hence, for CAR-T cell recipients with persistently positive nucleic acid amplification, viral sequencing is needed to surveil the emergence of dangerous variants of SARS-CoV-2 that may evade the both natural immunity and vaccine-induced immune responses, potentially leading to new outbreaks that result in increased treatment difficulty and higher mortality rates. It would be disastrous and must be prevented at all costs.

3. Assessment of patients before initiating CAR-T cell therapy

Given the underlying conditions and immune status of CAR-T cell recipients, they are at an increased risk of COVID-19. Therefore, before initiating CAR-T cell therapy, patients should be advised to adopt optimal hygiene practices to minimize the risk of contracting SARS-CoV-2. This includes regular handwashing, wearing masks, and practicing social distancing.¹⁴ In addition, screening and assessing the risk of infection from not only COVID-19 but also other respiratory viruses is necessary before proceeding with CAR-T cell therapy.¹⁵ It is also crucial to monitor COVID-19 nucleic acid at key intervals throughout the treatment process, specifically prior to T-cell collection, pre-conditioning, and CAR-T cell infusion.¹⁶ Ensuring a negative COVID-19 nucleic acid result at these stages is essential to safeguard the patient's health and the success of the therapy. Nasopharyngeal swabs are more sensitive than oropharyngeal swabs, especially in detecting infections in early and asymptomatic patients.⁵

4. The timing for initiating CAR-T cell therapy

For patients confirmed with COVID-19, delaying CAR-T cell therapy is necessary, with a typical suspension period of 14 – 21 days.¹⁷ For asymptomatic individuals, the suspension period can be appropriately shortened if the primary disease is progressing rapidly. Conversely, for severe or critically ill patients, the suspension can be appropriately extended if the primary disease is relatively stable.¹⁷ Collaboration from a multidisciplinary team is needed to balance the risks of delayed CAR-T cell therapy and SARS-CoV-2 infection to achieve the benefit maximization.

5. Management of COVID-19 in CAR-T cell recipients

According to the World Health Organization's classification criteria, the severity of COVID-19 is categorized into critical, severe, and non-severe stages.¹⁷ Treatment strategies for COVID-19 should be determined by the severity of the condition. For patients with non-severe COVID-19, early antiviral treatment can reduce the risk of disease progression to a severe stage. Oral antiviral agents such as Paxlovid, remdesivir, and azvudine should be considered, depending on the availability of these medications. Attention should be given to potential drug-drug interactions and drug toxicity, necessitating careful monitoring of hepatic and renal toxicity.¹⁸ The duration of antiviral treatment may be appropriately extended to align with individualized care, guided by the timing of the transition to negative in SARS-CoV-2 nucleic acid or antigen testing, as well as a thorough assessment of the patient's clinical symptoms and immune function. Patients with severe or critical COVID-19 may benefit from the combination of antivirals with supportive interventions such as systemic corticosteroids, anticoagulants, and/or immunomodulators.¹⁹ For example, dexamethasone and remdesivir have shown synergistic benefits for hospitalized patients who require oxygen therapy.²⁰ However, it is important to note that immunomodulators and anti-inflammatory drugs can be harmful in the early treatment of COVID-19 by suppressing the immune response and increasing viral load. For hospitalized patients, however, these drugs may work synergistically with antiviral drugs to reduce excessive inflammatory responses.

COVID-19 convalescent plasma could also be tried for severe or critical patients. However, there are no studies for the use of convalescent plasma in CAR-T cell recipients. Hence, the timing of infusions is determined by the clinician based on the patient's individual condition and viral load. In addition, the administration

of immunoglobulin to address complement deficiency in patients with hypogammaglobulinemia is necessary. COVID-19 infection can complicate the treatment of cytokine release syndrome further. Metagenomic next-generation sequencing is an effective method to uncover other potential pathogen infections that may not be detected using conventional testing methods during the peri-CAR-T cell therapy period.²¹ The immune status of patients significantly affects treatment responses and clinical outcomes. Herein, we emphasize individualized therapy, considering the patient's general condition, the severity of the disease, the urgency of treatment, and the viral load. This may require the collaboration of a multidisciplinary team, including oncologists, infectious disease specialists, and immunologists to develop the best treatment schedule. COVID-19 infection can also lead to post-acute sequelae in pulmonary and various extrapulmonary organ systems, lasting for 2 years or longer. Therefore, long-term follow-up and health management of CAR-T cell recipients is necessary.²²

For CAR-T cell recipients who are uninfected or have recovered from COVID-19, caution should still be taken against reinfection or breakthrough infection during the process of CAR-T cell therapy. Regular SARS-CoV-2 nucleic acid or antigen testing is needed. These individuals should continue preventive measures such as wearing masks, practicing social distancing, and avoiding crowded settings.

6. SARS-CoV-2 vaccination in CAR-T cell recipients

The specific challenges faced by CAR-T cell recipients in relation to COVID-19 vaccination include a diminished antibody response due to B-cell aplasia, which is a common side effect of CAR-T cell therapy.²³ This results in a lower seroconversion rate following vaccination, with some studies suggesting that patients receiving CAR T cell therapy, particularly those with B-cell related malignancies, are less likely to mount a humoral immune response.^{24,25} A systematic review and meta-analysis of 18 studies estimated a pooled humoral response rate of 28.2% among CAR-T cell recipients, indicating a significantly blunted vaccine response rate.²⁶ However, a large study has shown that these immunocompromised patients are capable of mounting significant T-cell responses against COVID-19. Robust cellular responses can be detected in the majority of CAR-T cell recipients, and spike-specific CD8⁺ T-cells seem to be significantly higher in the absence of a humoral response.²⁷ While CD8⁺ T-cells are associated with improved survival in B-cell depleted patients with hematologic malignancies and COVID-19, the precise protective role of T-cell responses remains uncertain.

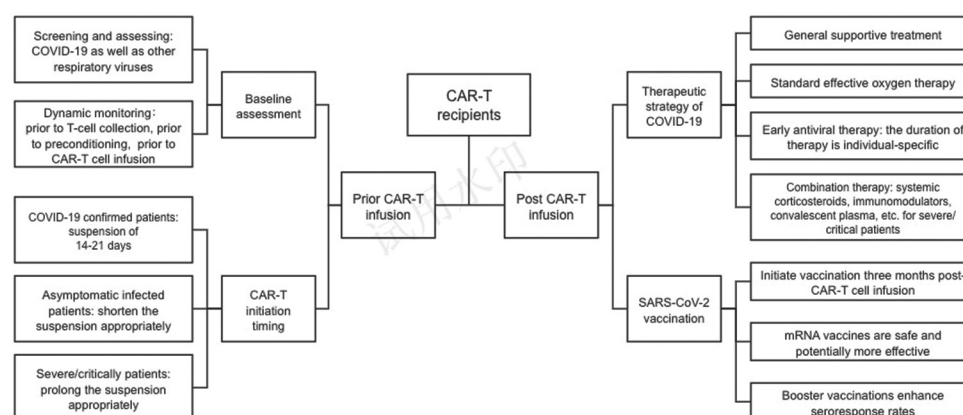


Figure 1. Management strategies for CAR-T cell recipients when encountering COVID-19

These findings underscore the complexity of vaccine responses in CAR-T cell recipients and highlight the need for a better understanding of the interplay between humoral and cellular immunity in this context. Regardless, there remains a clear consensus that vaccines are beneficial in preventing hospitalizations and deaths following SARS-CoV-2 infections.²⁸

Given the impaired humoral response, it is crucial to individualize the vaccination strategy for CAR-T cell recipients. The timing of vaccination is also important, with recommendations suggesting that vaccination should be initiated 3 months after treatment.²⁹ This allows for a balance between the potential immune response and the ongoing immune suppression effects of CAR-T cell therapy. In addition, mRNA vaccines have been shown to be safe and potentially more effective in this patient population, with a third dose improving the rate of seroconversion in patients who did not respond to the initial two doses. A fourth dose has also been found to be safe and could further increase antibody titers.³⁰

Past year, the XBB variant, a subtype of Omicron, became the dominant strain worldwide. EG.5, a subvariant of XBB.1.9.2, gained significant prevalence. As EG.5 continues to spread globally, some countries, such as the United States and the United Kingdom have identified it as a variant of concern.³¹ *In vitro* studies have shown that nirmatrelvir or ritonavir remains effective against XBB.³² The Chinese government has clearly indicated that vaccines containing the antigen component of the XBB variant are recommended as a priority. The recombinant trivalent COVID-19 vaccine (XBB+BA.5+Delta variant) is the first globally approved for emergency use against XBB and other variants.

Overall, while CAR-T cell recipients may not mount a robust antibody response to COVID-19 vaccines, the potential benefits of vaccination, including the induction of T-cell responses and the possibility of

improved seroconversion with additional doses, make it a recommended course of action for this vulnerable population. It is advised that CAR-T cell recipients receive the primary vaccination series and boosters as per the guidelines, with the understanding that larger prospective studies are needed to determine the optimal vaccine dosing strategies for this group.

7. Conclusion

CAR-T cell recipients continue to face significant challenges in the post-COVID-19 pandemic era. It should be noted that prevention is more important than treatment. Vaccination and daily non-pharmaceutical interventions against SARS-CoV-2 are the cornerstones of COVID-19 prevention. CAR-T cell recipients should be vaccinated with an updated booster. Once COVID-19 is contracted, early and prompt administration of antiviral drugs is crucial to reduce the risk of developing severe conditions. Current antiviral drugs remain effective against Omicron subvariants. The management strategies for CAR-T cell recipients infected with COVID-19 are summarized in [Figure 1](#). It is believed that, with the development of clinical trials and new drugs, and the accumulation of clinical practice experience, challenges faced by CAR-T cell recipients infected with COVID-19 will be substantially diminished in the future.

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Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

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