Supportive Care for Patients with Lymphoma Undergoing CAR-T-cell Therapy: the Advanced Practice Provider’s Perspective

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Abstract

Purpose of Review The purpose of our paper is to describe the all-encompassing supportive care for patients with relapsed or refractory lymphoma undergoing cellular therapy, with a focus on the advanced practice provider’s (APPs) perspective.

Recent Findings Chimeric antigen receptor-T (CAR-T) cell therapy has become more available for treating relapsed or refractory B-cell hematologic malignancies, requiring proficient and adequate treatment of side effects, complications, and infections that may occur during therapy. APPs often meet these patients during the initial referral and help to support them through the CAR-T cell therapy process.

Summary As APPs acquire a complete understanding and comprehensive knowledge of how to treat, support, and guide patients with B-cell malignancies through CAR-T cell therapy, they play a pivotal role in these patients throughout their treatment. Standardization of supportive care is paramount.

Keywords CAR-T cell therapy · COVID-19 · Supportive Care · Vaccinations

Introduction

Since first gaining Food and Drug Administration (FDA) approval in 2017, chimeric antigen receptor-T (CAR-T) cell therapy has become more available for treating relapsed or refractory B-cell lymphoma owing to its ability to induce sustained remissions [1]. Currently, four CAR-T cell constructs have achieved FDA approval for different lymphoma indications: lisocabtagene maraleucel, tisagenlecleucel, brexucabtagene autoleucel, and axicabtagene cileoleucel. As CAR-T cell therapy is becoming more widely commercially available and evaluated in multicenter clinical trials, the importance of providing comprehensive supportive care has become apparent. With the COVID-19 pandemic saturating overwhelmed health care systems, making sure CAR-T cell therapy recipients can safely receive optimal treatment is crucial to the viability of cellular therapy programs. Supportive care for CAR-T cell therapy via close monitoring and evaluation by a clinician includes assessing for signs of cytokine release syndrome (CRS), changes in neurological status, monitoring for infections, utilization of prophylactic antimicrobials, addressing hypogammaglobulinemia needs, and determining the appropriate immune reconstitution and post-CAR-T cell therapy vaccinations. Within this paper, we will specifically address the inherent complexities that SARS-CoV-2 (severe acute respiratory coronavirus 2) or COVID-19 (coronavirus disease 2019) has brought upon patients receiving cellular therapies.

Candidate Referral, Eligibility, and Therapy Initiation

Treatment centers that are authorized to prescribe cellular therapy may receive patient referrals from internal practice partners or outside sources, such as community oncologists...
or patients themselves. Expediting referrals from external sources may be accomplished by establishing a pre-screening workflow for obtaining records with a checklist of eligibility requirements. Additionally, immediate insurance verification upon referral identifies policies that lack specific benefits or require individual contract negotiations to circumvent any delays in formal evaluation and cell collection. A well-defined referral workflow reduces healthcare utilization of services needed for CAR-T cell therapy evaluation, avoids unnecessary travel to an authorized center, and allows dynamic and thorough communications with the referring physician for care planning.

The decision to treat a patient with CAR-T cell therapy should be made collectively by a multidisciplinary team at a designated center for CAR-T cell therapy [2••]. To be eligible, patients with B-cell lymphomas currently must have relapsed or refractory disease after at least two lines of standard chemotherapy [3]. Axicabtagene ciloleucel has been recently FDA approved in second-line therapy (after one line of standard chemotherapy) [4]. In addition to the patient’s medical history and physical condition being important factors in determining their suitability for treatment [5], other criteria to take into consideration include age, performance status, organ function, history of active malignancy, presence of CNS involvement by lymphoma, history of transplant or prior CAR-T cell therapy [6], history of autoimmune disease, current systemic immunosuppressive treatment, and existing or suspected infection [7••] including COVID-19.

At initial evaluation, patients meet with a hematologist to discuss eligibility, alternate treatment options, the process of CAR-T cell therapy, risks, and benefits and then will undergo a thorough screening process. Standard laboratory evaluations that are obtained include a complete blood count (CBC) with differential, comprehensive metabolic panel (CMP), lactate dehydrogenase (LDH), C reactive protein (CRP), ferritin, fibrinogen, and human chorionic gonadotropin quantitative pregnancy test for women of childbearing age. Infectious disease screening includes serological evaluation for human immunodeficiency virus, cytomegalovirus, and herpes simplex virus types 1 and 2 (Table 1). A COVID-19 history should include possible exposures, symptoms of infection, history of prior infection and treatment received, and vaccination status. Standard diagnostics workup testing includes an electrocardiogram, echocardiogram, pulmonary function test, positron emission tomography-computed tomography, and brain magnetic resonance imaging. We also assess for symptoms of COVID-19 at all relevant time points including apheresis, before lymphodepletion chemotherapy, and before CAR-T cell infusion. We perform Polymerase Chain Reaction (PCR) COVID-19 testing for all patients within 48 h of CAR T-cell administration. Once screening tests are reviewed, and the patient is deemed a candidate for CAR-T cell therapy, patients meet with several team members to further discuss the process and what to expect during therapy. Patients also undergo psychosocial evaluation and meet with a cellular therapy financial advisor. They attend a cellular therapy education class, which includes guidelines and restrictions for patients and visitors during the time of COVID-19. Regarding preventive measures, we limit in-person visits, when feasible, by using telemedicine, and contingency plans are developed if the patient and/or caregiver becomes infected by COVID-19 during the CAR T-cell process. Patients meet with a neuro-oncologist to establish a baseline neurological exam and discuss the potential for neurotoxicity and its treatment during CAR-T cell therapy. Once deemed eligible for CAR-T cell therapy, patients meet with the apheresis team, and undergo T-cell collection.

Scheduling of leukapheresis must be coordinated with the pharmaceutical company as timely manufacturing capacity is a current challenge in the availability of CAR-T cell therapies [2••]. The typical turnaround to manufacture the CAR-T cell therapy product is approximately 3–4 weeks [8]. Lymphodepletion chemotherapy is administered on day minus 5 to day minus 3 before the infusion of CAR-T cells. Lymphodepletion before CAR-T cell infusion creates a favorable environment for CAR-T cell expansion and survival. In addition, it can lead to the upregulation of tumor immunogenicity and improve overall disease control. Although fludarabine and cyclophosphamide are the most widely used lymphodepletion chemotherapies, other options include bendamustine and total body irradiation [2••]. Lymphodepletion chemotherapy further immunosuppresses these patients predisposing them to infections including COVID-19 and opportunistic infections common with low CD4 counts.

Patients were hospitalized for CAR-T cell infusion as part of most pivotal trials to monitor closely for side effects, toxicity, and complications; however, the safety and feasibility of outpatient infusion are being explored at some centers.

Table 1 Infectious disease screening and prophylaxis

| Screening                                      | Prophylactic medications                                      |
|-----------------------------------------------|---------------------------------------------------------------|
| Human immunodeficiency virus                  | Antivirals: consider for 1 year and/or until CD4 count > 200 |
| Cytomegalovirus IgG/IgM screening             | Antimicrobials: consider when ANC < 1.0 cells/mL              |
| Epstein Barr virus IgG/IgM screening          | Antifungals: consider when ANC < 1.0 cells/mL for prolonged period of time |
| Herpes simplex virus 1 and 2                  | SARS-CoV-2                                                   |
| Coccidiomycosis (if endemic)                  |                                                              |
| Pneumocystis jiroveci: consider until CD4 > 200 |                                                              |
Premedicating with an antihistamine and antipyretic before infusion may help prevent adverse reactions. Historically, corticosteroids have been avoided as they are lymphocytotoxic; thus, the initial concern was that they may impair CAR-T cell expansion and efficacy [2••]; although in the clinical trial ZUMA-1 cohort 6, prophylactic dexamethasone was able to demonstrate decreased severity of CRS and is now FDA approved before infusing axicabtagene ciloleucel along with early intervention with tocilizumab for CRS/ICANS [9]. Accurate assessment and prompt management of toxicities can mitigate adverse events associated with these potentially curative immunotherapies. The overall goal is to maximize the benefit of the cellular therapy while minimizing the risk of life-threatening complications, particularly severe CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) [10].

**CAR-T Toxicity and Supportive Care**

Our paper aims to focus on supportive care, rather than toxicity management, since managing CRS/ICANS associated with CAR-T cells has been described elsewhere including in the American Society for Transplantation and Cellular Therapy (ASTCT) guidelines [11]. CRS is triggered by the activation of T cells on the engagement of their CARs with cognate antigens expressed by tumor cells [10]. CRS has been observed in 42–92% of recipients receiving autologous anti-CD19-directed CAR-T cell therapy [12]. CRS can manifest as a variety of symptoms ranging from flu-like symptoms to more severe life-threatening manifestations of an overstimulated inflammatory response (hemophagocytic lymphohistiocytosis and macrophage activation syndrome-like response) (Fig. 1). Severe CRS is characterized by hypotension, circulatory shock, disseminated intravascular coagulation, and multi-organ system failure [13]. Serum biochemical parameters, including CRP, ferritin, and LDH [14], are often elevated in patients with CRS [12] and are monitored daily.

Patients undergoing CAR-T cell therapy remain at an increased risk of infection due to lymphodepletion chemotherapy, B-cell aplasia, and prolonged cytopenias; therefore, it is essential to broadly cover for possible infection empirically at the onset of fever. A general infectious disease workup is performed, including blood cultures, urinalysis and urine culture, chest X-ray, and nasopharyngeal swabs if patients have symptoms associated with an upper respiratory tract infection. Neutropenic patients are placed on broad-spectrum antimicrobials. If a source of infection has been identified, antimicrobials are tailored accordingly. Consultation with an infectious disease specialist should be considered to guide the escalation or de-escalation of antimicrobial therapy, particularly in high-risk patients [15]. For patients that remain febrile, despite negative blood cultures, evaluation for opportunistic infections should be prioritized, including COVID-19, viral and fungal infections.
which could reactivate in the setting of severe immunosuppression in patients that have had COVID-19 shortly before their admission. The ASTCT guidelines have become the most widely used standard for grading and treating CAR-T-associated toxicity [16•]. Toxicity management guidelines may vary slightly with each FDA-approved CAR-T cell therapy product, based on package insert recommendations and Risk Evaluation and Mitigation Strategy (REMS) programs. When patients experience more severe CRS, supportive care is initiated including fluid resuscitation, vasopressors for hypotension, supplemental oxygen as needed for hypoxia, the interleukin-6-receptor blocking antibody tocilizumab [17], steroids, and potentially other immunosuppressants in refractory cases [13], which can lead to further immunosuppression and blunt the typical symptoms that alert us that an infection is present.

A rare but potentially fatal complication of CAR-T therapy is hemophagocytic lymphohistiocytosis (HLH) or macrophage activation-like syndrome (MAS), characterized by severe immune activation, and immune-mediated multi-organ failure. Diagnosis is difficult in the context of CRS as features of HLH/MAS and CRS often overlap [18]. Traditional diagnostic criteria for HLH/MAS include fever, splenomegaly, cytopenias, hypertriglyceridemia, and hypofibrinogenemia [19]. Daily monitoring of fibrinogen and coagulation studies is also recommended as some of these patients develop disseminated intravascular coagulopathy (DIC). Clinicians should be suspicious of HLH/MAS if CRS is resolving and ferritin continues to rise, especially if such serological marker value is greater than 10,000 mcg/L, if there is evidence of new cytopenias without any other explanation, or if the patient is developing grade 3 or greater organ toxicities [19]. Effective treatment of HLH/MAS requires aggressive immunosuppression to control the hyperinflammatory state. IL-6 blockade with corticosteroids remains the cornerstone of treatment and should be started at a time of high clinical suspicion of HLH/MAS. Additional therapies have been used, including etoposide, ruxolitinib, cyclophosphamide, siltuximab (an anti-interleukin 6 monoclonal antibody), and/or anakinra (an interleukin 1 receptor antagonist) [18], which could again further immunosuppress our patients putting them at risk for infectious complications.

Another common complication of CAR-T therapy is ICANS, occurring in about 36–64% of patients, depending on the construct used [20]. Upon admission, neurology is consulted before infusion of the CAR-T cell therapy, so that they can perform a complete neurological baseline exam, including a Mini-Mental Status Exam. Clinicians, as well as nurses, monitor the neurological status every 4 h with the 10-point cognitive skill assessment called the immune cell effector encephalopathy (ICE) screening tool. Prophylactic anti-seizure medications may be considered per institutional guidelines. Mild symptoms of neurotoxicity include expressible aphasia, confusion, and tremors. Deterioration in handwriting is an early predictor of neurotoxicity; therefore, daily writing tests for the first month following CAR-T cell infusion can be used as a simple tool to screen for ICANS [2••]. As symptoms become more severe, patients can be agitated, obtunded, and rarely develop seizures [13]. The ASTCT guidelines have become a widely used standard of practice when assessing, grading, and treating ICANS. Neurotoxicity can have a biphasic clinical presentation with the initial neurological symptoms accompanying classical CRS, and a second phase occurs later without obvious clinical CRS [21]. If initiated, anti-epileptic medications such as levetiracetam should be continued until the resolution of ICANS and tapered over the following 1–2 weeks unless seizures were documented. Due to the potential for delayed neurotoxicity, it is asked that patients do not drive until they are cleared by their medical provider 8 weeks post-infusion.

Potential life-threatening manifestations of ICANS include cerebral edema or multifocal hemorrhage. The severity is often correlated with increased CRP, ferritin, and IL-6 [2••]. If there is clinical suspicion, a CT head should be performed to rule out cerebral edema or hemorrhage; however, the role of a CT scan is limited. Transfer to the ICU may be indicated as patients may need to be intubated for airway protection. Neurosurgery should be consulted in patients with concerns for increased intracranial pressure. High-dose steroids are the treatment of choice, along with aggressive supportive care.

Cytopenias are commonly seen following CAR-T cell therapy and can persist in over 50% of patients beyond day 30 after infusion [22]. Alterations of the coagulation cascade following CAR-T cell infusion are also common and include prolongation of the prothrombin time and activated partial thromboplastin time, D-dimer elevation, low fibrinogen, and DIC can occur. Patients are transfused to keep their hemoglobin greater than 8.0 g/dL (normal range 12 to 17.5 g/dL) and platelet count greater than 20,000 per mL of blood (normal range 150,000–450,000 per mL of blood), as long as there is no active infection or active bleeding. Cryoprecipitate is transfused to keep fibrinogen > 100 mg/dL (normal range 200–400 mg/dL). These transfusion cut-offs may vary based on institutional guidelines and may further be individualized based on each patient’s clinical characteristics (Table 2). Filgrastim can be considered when the absolute neutrophil count (ANC) is < 1000 cells per mL (normal range is 2500 to 6000 cells per mL) given the possibility of CRS/ICANS exacerbation.

### Infection Monitoring and Prophylaxis

Patients undergoing CAR-T cell therapy may have prolonged or intermittent neutropenia, B-cell aplasia/hypogammaglobulinemia, and low CD4 count increasing their risk of
opportunist infections or viral reactivations. Fever is common; however, confirmation of a bacterial pathogen via positive blood cultures is relatively uncommon but may occur within the first 2 weeks of CAR-T infusion [23]. Although most infections occur within the first 30 days after CAR-T cell infusion, recipients are at an increased risk of a range of infections at different stages of their treatment course, and appropriate antimicrobial coverage is required [24•] (Table 2). Routine antiviral prophylaxis should be started in all patients and continued for 12 months post-infusion. For neutropenic patients with an ANC <1000 cells/μL, prophylactic antibiotics are given based on site-specific guidelines. Fungal prophylaxis should also be considered depending on the duration and severity of neutropenia. Pneumocystis jirovecii prophylaxis should be continued until the CD4 count is over 200 cells/mm. IgG should be monitored monthly, and replacement should be considered for an IgG level <400 mg/dL, particularly in the setting of severe or recurrent infections, though this is controversial.

Once patients are discharged, it is recommended that they stay within 30 min of the hospital to be closely monitored. All patients post-CAR-T cell therapy return for at least weekly visits through day +30, then monthly visits through day +100, or as clinically indicated. Patients are released back to their community oncologist when clinically stable after day +100, but our team remains closely involved. For patients that live out of state, or whose primary oncologists are outside of our network, our center continues to assess response via review of outside records for Center for International Blood and Marrow Transplant Research (CIBMTR) reporting. Furthermore, we provide detailed instructions both to patients and primary oncologists regarding recommendations for monitoring and supportive care.

Patients who have undergone a hematopoietic stem cell transplant (HSCT) before immune effector cell (IEC) infusion and did not complete cellular therapy immunizations post-HSCT will receive an abbreviated immunization schedule after IEC infusion. There is questionable efficacy of vaccines in patients with B-cell aplasia and the lack of standardized testing for immune reconstitution following CAR-T therapy. Inactivated vaccines may be administered starting 6 months post-CAR-T infusion and include the hepatitis B vaccine, pneumococcal conjugate, and herpes–zoster vaccinations. Live vaccines are contraindicated in immunosuppressed patients. The inactivated influenza vaccine may be given post-infusion anytime from October through June. COVID-19 vaccination recommendations are discussed separately.

### COVID-19

The COVID-19 pandemic presents unprecedented challenges to delivering cellular therapy to patients with hematologic malignancies. Delaying cellular therapy due to the COVID-19 pandemic is not a realistic option for patients with aggressive lymphomas given concerns regarding disease progression and mortality [24]. Despite the increased risk of complications with cellular therapies, CAR-T has continued to be prescribed around the globe [25•]. Relaxed restrictions on the use of telemedicine from the Centers for Medicare and Medicaid Services have allowed the initial consultation and patient education to be delivered in a safe and timely manner virtually. At our institution, CAR-T cell therapy patients are tested for COVID-19 48–72 h before apheresis and before starting lymphodepletion chemotherapy, and then every 7 days while inpatient after receiving their infusion. Institutional guidelines may differ regarding COVID-19 prevention and treatment.

Cellular therapy recipients are highly susceptible to COVID-19 infection [26] due to their compromised immune system and high likelihood of inefficient response to available vaccines [27]. Studies from the European Hematology Association found that the COVID-19 mortality rate was 33% in patients treated with CAR-T therapy [28, 29]. Patients treated with anti-CD20 monoclonal antibodies have lower seroconversion rates, leading to prolonged viral shedding after COVID-19 [30]. As the COVID-19 pandemic rapidly evolves, clinicians must frequently re-evaluate guidelines for COVID-19 management, particularly regarding updates for cellular therapy patients. The treatment of COVID-19 in a CAR-T cell recipient should be done in coordination with infectious disease experts.

Patients who test positive for COVID-19 before the infusion are delayed for a minimum of 14 days [31] from symptom resolution [24]. For CAR-T recipients who are positive for COVID-19 infection, remdesivir (Table 3), the first antiviral agent to receive FDA approval for hospitalized COVID-19 patients, is the most frequently used inpatient treatment, though a shorter course can also be given outpatient. Antiviral agents that inhibit SARS-CoV-2 replication offer another form of protection that could be unaffected by mutations that may compromise monoclonal antibodies

| Table 2  | Supportive care |
|----------------------------------|
| **Supportive care** | |
| Red cell transfusion: maintain hemoglobin >8.0 g/dL. | |
| Platelet transfusion: maintain platelet count >20,000 per mL of blood† | |
| Cryoprecipitate transfusion: maintain fibrinogen >100 mg/dL | |
| Filgrastim injection: should be considered when absolute neutrophil count is <1.0 cells/mL† | |

*Platelet threshold should be increased per institutional guidelines in the setting of active bleeding or undergoing invasive procedures

**Only when there is no evidence of active cytokine release syndrome
| Drug          | Mechanism of action                                                                                                                                                                                                 | Drug-drug interaction                                                                                     | Approval use                                                                                                                                                                                                 |
|--------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Remdesivir   | Acts to inhibit the SARS-CoV-2 RNA-dependent RNA polymerase (inhibiting the ability of viral replication)                                                                                                         | Chloroquine and hydroxychloroquine sulfate decrease the effects of remdesivir by unspecified interaction mechanisms. Avoid or use an alternative drug. Remdesivir increases the effects of warfarin by an unspecified interaction mechanism. Use caution/monitor. | Indicated for adults and pediatric patients (over 12 years old weighing at least 40 kg) requiring hospitalization for COVID-19. Can be utilized in the outpatient setting for a shorter course duration of 3 days |
| Nirmatrelvir/Ritonavir | Nirmatrelvir inhibits the main protease of SARS-CoV-2 and blocks viral replication. Ritonavir is a potent cytochrome P450 3A4 inhibitor resulting in a long half-life when co-administered with nirmatrelvir. | Contraindicated drugs that either decrease/increase the level or effect of nirmatrelvir/ritonavir by affecting hepatic/intestinal enzyme CYP3A4 metabolism include the following: alfuzosin, amiodarone, carbamazepine, clozapine, colchicine, ergotamine, flecainide, fosphenytoin, lovastatin, lurasidone, meperidine, methylergonovine, midazolam, phenytoin, pimozide, piroxicam, primidone, propafenone, quinidine, ranolazine, rifampin, sildenafil, simvastatin, St. John’s Wort, and triazolam. | Treatment of mild to moderate COVID-19 in adults and pediatric patients (over 12 years old weighing at least 40 kg) at high risk for progression to severe COVID-19 including hospitalization or death |
| Tixagevimab/Cilgavimab | Recombinant human IgG1-kappa mAbs that bind to non-overlapping regions on spike protein receptor-binding domain of SARS-CoV-2 modified to extend half-life to greater than 80 days. | No known drug-to-drug interactions. | Pre-exposure prophylaxis of COVID-19 in adults or pediatric patients (over 12 years old weighing at least 40 kg) who are not currently infected and without recent exposure and have moderate-severe immune compromise due to medical condition or medications and may not mount a response to a vaccine |
| Molnupiravir | Metabolized to cytidine nucleoside analog and phosphorolyated to active ribonucleoside triphosphate incorporated into SARS-CoV02 RNA resulting in viral genomic errors and inhibition of viral replication. | No known drug-to-drug interactions. | Treatment of mild to moderate COVID-19 in adults and pediatric patients (over 12 years old weighing at least 40 kg) at high risk for progression to severe COVID-19 including hospitalization or death |
| Sotrovimab    | Recombinant human IgG1-kappa mAb that binds to conserved epitope on spike protein receptor-binding domain of SARS-CoV-2                                                                                              | No known drug-to-drug interactions. | Treatment of mild to moderate COVID-19 in adults and pediatric patients (over 12 years old weighing at least 40 kg) at high risk for progression to severe COVID-19 including hospitalization or death |

List of interactions is not comprehensive.
Monoclonal antibodies have been shown to lower the risk of COVID-19 hospitalizations in patients with cancer [33]; however, as the COVID-19 variants evolve, we need to continually evaluate the efficacy of these therapies. Newer agents such as nirmatrelvir/ritonavir has shown benefit in patients with mild to moderate cases of COVID-19 at high risk for severe illness. This is indicated in immunocompromised patients and can be considered in CAR-T cell therapy recipients who remain outpatient. Nirmatrelvir impacts cytochrome P450, family 3, subfamily A (CYP3A); therefore, drug interactions should be considered when starting the medication. Tixagevimab-cilgavimab is a monoclonal antibody therapy available under emergency use authorization (EUA) for patients 12 years and older who are not currently infected with SARS-CoV-2, and who have moderate to severe immune-compromised status due to a medical condition or recipient of immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination (such as CAR-T patients) [34]. Molnupiravir has been expected to retain activity against the Omicron variant and has been approved for EUA for treatment of mild-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19 infection; however, it should only be used when an alternative COVID-19 treatment option authorized by the food and drug administration (FDA) is not accessible due to lower efficacy in preventing hospitalization [34]. Sotrovimab is an investigational SARS-CoV-2 neutralizing monoclonal antibody that has been approved for emergency use authorization (EUA) and is indicated in non-hospitalized patients with mild disease, including those post-CAR-T therapies. CAR-T cell therapy recipients have profound immune dysregulation (B cell aplasia, low IgG levels, and low CD4 counts) and may shed SARS-CoV-2 for months [35] after symptom onset, consistent with persistent infection [25]. Studies have shown that some vaccinated patients who received cellular therapies were able to recover from COVID-19 infection and some have evidence of antibody response to vaccination [36, 37].

Current National Comprehensive Cancer Network (NCCN) guidelines suggest restarting the COVID-19 3-shot vaccination series 3 months after CAR-T cell therapy, plus a booster (4th dose) [38] (Fig. 2). The BNT162b2 (Pfizer/BioNTech) and the mRNA-1273 (Moderna) COVID-19 vaccines have been demonstrated in large phase III clinical trials to be more than 90 percent effective at preventing confirmed COVID-19 illness and severe infections in immunocompetent hosts [39]. Oncology patients were largely excluded from the initial clinical trials [40]. Based on a phase 1 trial of the mRNA SARS-CoV-2 vaccines, peak neutralizing antibodies developed 7 to 14 days after the second dose of

Fig. 2 COVID-19 vaccination recommendations for CAR T-cell recipients. The asterisk “*” represents the definition of immunocompromised patient which includes congenital or acquired immunodeficiencies, Human Immunodeficiency Virus infection, malignancy, solid organ transplant, patients on any immunosuppressive medication, radiation therapy, all hematologic malignancies, patients who have received chemotherapy medications in the last 30 days, and or bone marrow transplant or cellular therapy recipients. The two asterisks “**” represent the third booster doses which are approved for patients 12 and older. Boosters are currently only approved for those 18 and older for mRNA-1273 and INJ-78436735 or 16 and older for BNT162b2. The CDC has recently updated its guidelines to recommend a fourth booster dose in patients that are immunocompromised...
the vaccine without prior infection [41••]. Willing CAR-T cell therapy recipients should be offered the COVID-19 vaccine before therapy and allowed at least 2 weeks after the second dose to allow memory T-cell formation [41••]. We support early access to vaccines for CAR-T cell recipients due to their extreme vulnerability, along with their caregivers, family, and household contacts [42]. Many patients with hematologic malignancies will have a suboptimal response to the vaccine due to impaired B-cell function (particularly those in early post-cellular therapy); therefore, continued vigilance with aggressive infection prevention (i.e., masks, social distancing, hand hygiene) and control measures is of critical importance in CAR-T therapy recipients [25•]. Although controversial, serological testing after COVID-19 vaccination may provide additional information to the individual patient and may aid in determining the timing and efficacy of booster doses [43]; nevertheless, this has not been standardized. The third dose of either mRNA vaccine has been approved by both the FDA and the Center for Disease Control (CDC) for immunocompromised patients at least 28 days from the second dose. The third dose is considered part of the original series, not a booster dose. The recommendation was based on waning protective antibodies over time in patients with hematologic malignancies [41••]. Moderately to severely immunosuppressed patients are eligible for a booster dose of the BNT162b2 and/or the mRNA-1273 COVID-19 vaccine 3 months after completing the three-shot initial series. Patients who received the JNJ-78436735 vaccine (Johnson and Johnson) are eligible for an additional dose at least 28 days after the first dose. A booster dose is recommended at least 2 months after the second dose and must be either the BNT162b2 and/or the mRNA-1273 vaccine [44•••].

Tixagevimab-cilagamab has been approved for EUA in patients who are currently not infected by SARS-CoV-2 and who have moderate to severe immune compromise thus felt not to mount an appropriate response to COVID-19 vaccination. In randomized clinical trials, monoclonal antibodies used to treat COVID-19 infections, including tixagevimab-cilagamab, had between 70 and 86% efficacy in reducing hospitalizations and death in high-risk and immunosuppressed patients [45]. Tixagevimab-cilagamab may be a better option post-CAR-T for patients than revaccination if they have no detectable B cells or severe hypogammaglobulinemia. The therapeutic landscape of COVID-19 continues to evolve rapidly.

Conclusion

Patients undergoing CAR-T cellular therapies experience immunosuppression from prolonged neutropenia, low CD4 count, B-cell aplasia, and hypogammaglobulinemia, increasing their overall risk of infections. The COVID-19 pandemic has brought upon us unprecedented challenges for immunocompromised patients. With the ongoing COVID-19 pandemic, it is pertinent to ensure that CAR-T cell therapy recipients can safely receive optimal supportive treatment. Infection prevention, prophylactic medications, and COVID-19 vaccination have helped ensure that patients with relapsed or refractory lymphoma are still able to undergo cellular therapy and remain safe from severe infection.

Author Contribution All co-authors reviewed and approved the paper while contributing equally.

Declarations

Competing Interests GG Consulting—Strategix, The Lynx Group, Incyte, CTI BioPharma. JM Consulting—Pharmaceuticals/Abbvie, Bayer, Gilead/Kite Pharma, Pfizer, Janssen, Juno/Celgene, BMS, Kyowa, Alexion, Fosunite, Innovent, Seattle Genetics, Debiopharm, Karyopharm, Genmab, ADC Therapeutics, Epizyme, Beigene, Servier, Novartis, Morphosys/Incyte; Research funding—Bayer, Gilead/Kite Pharma, Celgene, Merck, Portola, Incyte, Genentech, Pharmacies, Seattle Genetics, Janssen, Millennium. Honoraria from Targeted Oncology, OncView, Curio, Kyowa, Physicians Education Resource, and Seattle Genetics; Speaker’s bureau—Gilead/Kite Pharma, Kyowa, Bayer, Pharmacies/Janssen, Seattle Genetics, Acrotech/Aurobindo, Beigene, Verastem, AstraZeneca, Celgene/BMS, Genentech/Roche. JEC Consulting—FATE therapeutics, Kite Pharmaceuticals.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (XUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncology. 2022;1:91–103. https://doi.org/10.1016/S1470-2045(21)00591-X
2. Yakoub-Agha I, Chabannon C, Bader P, et al. Management of adults and children undergoing chimeric antigen receptor T-cell therapy: best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EMBT (JACIE). Haematologica. 2020;105:297–316. https://doi.org/10.3324/haematol.2019.229781. (This editorial highlights the practical recommendations for CAR-T cell therapy patients, including how to manage and treat CRS and ICANS.)
3. Nastoupil LJ, Jain MD, Feng L, et al. Standard-of-Care Axicabtagene ciloleucel for relapsed or refractory large B-cell mature

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lymphoma: results from the US Lymphoma CAR T Consortium. Clin Oncol. 2022;27:3119–28. https://doi.org/10.10120/JCO.19.02104.

4. Locke Frederick L, Miklos David B, Jacobson Caron A, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. N Engl J Med. 2022;386:640–54. https://doi.org/10.1056/NEJMoa2116133.

5. Neelapu SS, Locke FL, Lekakis LJ, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. New Engl J Med. 2017;26:2531–44. https://doi.org/10.1056/NEJMoal703447.

6. Spiegel JY, Dahiya S, Jain MD, et al. Outcomes of patients with large B-cell lymphoma progressing after axicabtagene ciloleucel therapy. Blood. 2021;13:1832–5. https://doi.org/10.1182/blood.2020006245.

7. Lee Daniel W, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Guideline. 2019;25:625–38. https://doi.org/10.1182/bjmm.20190221.

8. Cassidy, Sorcha; Webster, Rachel; and D. Phil. 2020. CAR T-Cell Therapy in non-Hodgkin’s lymphoma: where do we go from here? Cell and gene. https://www.cellandgene.com/doc/car-t-cell-therapy-in-non-hodgkin-s-lymphoma-where-do-we-from-here-0001.

9. O Oluwol Alekzen Krimo B Aufbaddelh Javier Munoz et al Prophylactic corticosteroid use in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. Bri J Haematol 2021;194:690 700 https://doi.org/10.1111/bjh.175257.

10. Neelapu Sattva S, Summala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy – assessment and management of toxicities. Nature. 2018;15:47–62. https://doi.org/10.1038/nrclee nonec.2017.148.

11. Pennisi M, Jain T, Santomasso B, et al. Comparing CAR T-cell toxicity grading systems: application of the ASTCT grading system and implications for management. Blood Adv. 2020;4:675–86. https://doi.org/10.1182/bloodadvances.2019000952.

12. Hong Ruimin Hu, Yongxian, and Huang He. Biomarkers for chimeric antigen receptor T cell therapy in acute lymphoblastic leukemia: prospects for personalized management and prognostic prediction. Frontiers in Immunology. 2021; 12. https://doi.org/10.3389/fimmu.2021.627764.

13. Morris, Emma; Neelapu, Sattva; Giavridis, Theodoros; and Michel Sadelain. 2021. Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. Nature Rev Immunol.https://doi.org/10.1038/s41577-021-00547-6

14. Greenbaum U, Strati P, Saliba RM, et al. CRP and ferritin in addition to the EASIX score predict CAR-T related toxicity. Blood Adv. 2021;5(14):2799–806. https://doi.org/10.1182/bloodadvances.2021004575.

15. Hill JA, Seo SK. How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies. Blood. 2020;136:925–35. https://doi.org/10.1182/blood.2019004000.

16. Lee, Daniel; Santomasso, Bianca; Locke, Frederick; et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Transplantation and Cellular Therapy. 2018. Doi: https://doi.org/10.1016/j.bbmt.2018.12.758. (These are Guidelines for grading and treating CRS and ICANs.)

17. Si S, Teachey D. Spotlight on tocilizumab in the treatment of CAR-T-cell-induced cytokine release syndrome: clinical evidence to date. Ther Clin Risk Manag. 2020;16:705–14.

18. Ahmed S, Furqan F, Strati P, et al. Haemophagocytic lymphohistiocytosis (HLH) in patients with large B-cell lymphoma treated with standard of care (SOC) axicabtagene ciloleucel (Axi-cel). J Clin Oncol. 2020;38:8057. https://doi.org/10.1200/JCO.2020.38.15_suppl.8057.

19. RD Sandler RS Tattersall H Schoemans et al Diagnosis and management of HLH/MAS following HSCT and CAR-T cell therapy in adults: a review of the literature and a survey of practice with EBMT centers on behalf of the Autoimmune Disease Working Party (ADWP) and Transplant Complications Working Party (TCPW) Front Immunol 2022 11https://doi.org/10.3389/fimmu.2020.00524.

20. Belin C, Devic P, Antoine C. Description of neurotoxicity in a series of patients treated with CAR-T cell therapy. Scientific Reports. 10. https://doi.org/10.1038/s41598-020-76055-9.

21. Chavez J, Jain M, Kharfan-Dabaja M. Cytokine release syndrome and neurologic toxicities associated with chimeric antigen receptor T-cell therapy: a comprehensive review of emerging grading models. Hematol Oncol Stem Cell Ther. 2020;13:1–6. https://doi.org/10.1016/j.hemotec.2019.05.005.

22. Irrham U, Osman K. Cytopenias following CAR-T cell therapy – a single center experience. Biol Blood Marrow Transplant. 2020;26:S260. https://doi.org/10.1016/j.bmt.2019.12.422.

23. Stewart AG, Henden AS. Infectious complications of CAR T-cell therapy: a clinical update. Ther Adv Infect Dis. 2021;8:1–11. https://doi.org/10.1177/2099361211036773.

24. Bachanova V, et al. Chimeric antigen receptor T-cell therapy during the COVID-19 pandemic. Biol Blood Marrow Transplant. 2020;7:1239–46. https://doi.org/10.1016/j.bmt.2020.04.008.

25. Mushtaq MU, Shahzad M, Chaudhary SG, et al. Impact of SARS-CoV-2 in hematopoietic stem cell transplantation and chimeric antigen receptor T cell therapy recipients. Transplant Cell Therapy. 2021;27:796e1–7. (This study looked at HSCT patients and CAR-T cell patients who had COVID, the complications they experienced, and how they were treated)

26. Dulery R, Lamure S, Heuso T, et al. Prolonged in-hospital stay and higher mortality after Covid-19 among patients with non-Hodgkin lymphoma treated with B-cell depleting immunotherapy. Am J Hematol. 2021;96:934–44. https://doi.org/10.1002/ajh.26209.

27. N Agrawal R Singh SK Sharma et al Outcomes of COVID-19 in hematopoietic stem cell transplant recipients: multicenter retrospective analysis Nature Publ Health Emerg Collect 2022;1-6https://doi.org/10.1007/s12288-021-01472-3

28. A Busca J Salmono-Garcia L Pagano et al 2021 COVID-19 and CAR-T cells: current challenges and future directions a report from the EPICOVIDEHA survey by EHA-IDWP Blood Advhttps://doi.org/10.1182/bloodadvances.2021005616.

29. Vjenthia A, Gong IY, Fatizetto B, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systemic review and meta-analysis of 337 patients. Blood. 2020;136:2881–92. https://doi.org/10.1182/blood.2020008824.

30. Spanjaar AM; Ljungman P, Miekle S, et. al. Poor outcome of patients with COVID-19 after CAR T-cell therapy for B-cell malignancies: results of a multicenter study on behalf of the European Society for Blood and Marrow Transplantation (EBMT) Infectious Disease Working Party and the European Hematology Association (EHA) Group. Leukemia. 2021;35:3585–3588 https://doi.org/10.1038/s41375-021-01466-0

31. Abassi J. Prolonged SARS-CoV-2 Infection in a CAR T-cell therapy recipient. JAMA. 2021;10:924. https://doi.org/10.1001/jama.2021.2493.

32. Corey L, Beyrer C, Rolland M, et al. SARS-CoV-2 Variants in hematopoietic stem cell transplant recipients: multicenter report from the EPICOVIDEHA survey by EHA-IDWP Blood Advhttps://doi.org/10.1182/bloodadvances.2021005616.

33. Corti D, Purcell LA, Veesler D, et al. Tackling COVID-19 with neutralizing monoclonal antibodies. Cell. 2021;184:3086–108. https://doi.org/10.1016/j.cell.2021.05.005.
34. Food and Drug Administration. Frequently Asked Questions on the Emergency Use Authorization for Evusheld (tixagevimab-coformulated with cilgavimab) for Pre-exposure Prophylaxis (PrEP) of COVID-19. February 24, 2022. https://www.fda.gov/media/154703/download
35. Aydillo T, Gonzalez-Reiche AS, Obla A, et al. Shedding of viable SARS-CoV-2 after immunosuppressive therapy for cancer. NEJM. 2020;383:2586–8. https://doi.org/10.1056/NEJMc2031670.
36. Shah GL, DeWolff S, Lee YJ, et al. Favorable outcomes of COVID-19 in recipients of hematopoietic cell transplantation. J Clin Investig. 2020;126:6656–67. https://doi.org/10.1172/JCI141777.
37. Liebers N, Speer C, Dietrich S, et al. Humoral and cellular responses after COVID-19 vaccination in anti-CD20-treated lymphoma patients. Blood. 2021;139(1):142–7. https://doi.org/10.1182/blood.2021013445.
38. National Comprehensive Cancer Network (NCCN). 2022. COVID-19 resources and guidelines. https://www.nccn.org/covid-19. (These are guidelines for COVID-19 treatment in immunocompromised patients.)
39. Maneikis K, Sablauskas K, Kryzauskaite L, et al. Immunogenicity of the BNT162b2 COVID-19 mRNA vaccine and early clinical outcomes in patients with hematological malignancies in Lithuania: a national prospective cohort study. Lancet Hematol. 2021;8:e583–592. https://doi.org/10.1016/S2352-3026(21)00169-1.
40. Sharma A, Bhatt NS, Chemaly RF, et al. Clinical characteristics and outcomes of COVID-19 in hematopoietic stem-cell transplantation recipients: an observational cohort study. Lancet Hematol. 2021;8:185–93. https://doi.org/10.1016/S2352-3026(20)30429-4.
41. Khawaja MD, Fareed; Chemaly MD, Roy F.; Dadwal MD, Sanjeet; et al. September 29, 2021. ASH-ASTCT COVID-19 Vaccination for HCT and CAR T cell recipients: Frequently Asked Questions. American Society of Hematology. https://www.hematology.org/covid-19/ash-astct-covid-19-vaccination-for-hct-and-car-t-cell-recipients (This article outlined the COVID-19 vaccination schedule for immunocompromised patients and vaccination timing in immunocompromised patients who received monoclonal antibodies for prevention or treatment of COVID-19.)
42. Sun C, Pleyer C, Wiestner A. COVID-19 vaccines for patients with haematological conditions. Lancet Haematol. 2021;8(5):e312–4. https://doi.org/10.1016/S2352-3026(21)00073-9.
43. Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood. 2021;137:3165–73. https://doi.org/10.1182/blood.2021011568.
44. Leukemia & Lymphoma Society (LLS). Study from the Leukemia & Lymphoma Society shows COVID-19 vaccine is safe but 25% of blood cancer patients do not produce detectable antibodies. 2022. https://www.lls.org/news/study-leukemia-lymphoma-society-shows-covid-19-vaccine-safe-25-blood-cancer-patients-do-not. (The Leukemia and Lymphoma Society has up-to-date guidelines for COVID-19 vaccinations for CAR-T cell recipients and their family members.)
45. Gentile I, Moriello N. COVID-19 prophylaxis in immunosuppressed patients: beyond vaccination. PLoS Med. 2022;19(1):e1003917. https://doi.org/10.1371/journal.pmed.1003917.
46. Sharma N, Reagan PM, Liesveld JL. Cytopenia after CAR-T cell therapy—a brief review of a complex problems. Cancers. 2022;14:1501. https://doi.org/10.3390/cancers14061501.
47. Jacobson, C; Locke, FL; Ghobaidi, A; Munoz, J; et. al. Hematology disease topics and pathways: biological therapies, adults, lymphomas, non-Hodgkin lymphoma, B cell lymphoma, chimeric antigen receptor (CAR)-T cell therapies, diseases, immune mechanism, therapies, lymphoid malignancies, biological processes, study population. ASH oral posters and abstracts (2021). https://ash.confex.com/ash/2021/webprogram/Paper14807.html.
48. Locke FL, Ghabadi A, Munoz J, Neelapu SS, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicenter, phase 1–2 trial. Lancet Oncol. 2019;20:31–42. https://doi.org/10.1016/S1470-204X(18)30864-7.

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