Infection Associated with the Use of CAR T Cells

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Introduction

Adoptive immunotherapy using targeted chimeric antigen receptor (CAR)-modified cells is a novel therapeutic approach with the potential to revolutionize the treatment of patients with several different medical conditions. CAR-modified T cells targeting the B-cell-specific antigen CD19 have been studied in several clinical trials and have demonstrated high rates of complete remission in patients with relapsed or refractory B-cell malignancies, including acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and non-Hodgkin lymphoma (NHL).

As CAR T cells are not a first-line therapy, most patients receiving them have a baseline immunosuppressed status due to previous therapies and baseline malignancy. Additionally, lymphodepletion chemotherapy is administered prior to CAR T-cell therapy, causing profound cytopenias and mucosal barrier dysfunction. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are frequent complications mediated by the elevation of proinflammatory cytokines which take place within the first weeks after CAR T-cell infusion. These life-threatening conditions are often indistinguishable from infections and sepsis, presenting with fever, tachycardia, tachypnea, and hypotension, as well as elevated inflammatory reactants. Intensive care unit admission (ICU) is frequent in this context. Moreover, the treatment of such complications is quite different from that of infections, requiring immunosuppressant therapy mainly with tocilizumab (humanized interleukin-6 receptor monoclonal antibody) and corticosteroids. Finally, CD19 CAR T cells can also deplete nonmalignant B-cells, resulting in varying degrees of B-cell aplasia and hypogammaglobulinemia.

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In this complex scenario, CAR T-cell recipients are at high risk of infectious complications, and their management regarding screening strategies, prophylaxis, empirical treatments, and de-escalation strategies is challenging. Due to the novelty of this treatment, knowledge on this topic is scarce and most recommendations are based on expert opinion. In this chapter we will briefly review the mechanism of action of CAR T-cell therapy and its main complications, as well as the different infectious complications and possible management strategies within this complex setting. Table 17.1 describes the main studies analyzed in the chapter.

Table 17.1 Main studies evaluating infectious complications in patients receiving CAR T-cell therapy

Study type and hematological malignancy	n	Prior HSCT	Median prior lines of treatment	Main results	Infection severity	Reference and year of publication[a]
Phase I/II study 47 B-ALL, 24 CLL, 62 NHL	133	38%	4	Days 0–28: 23% infections; infection density: 1.19 per 100 days at risk Days 29–90: 14% infections; infection density: 0.67 per 100 days at risk RF for infection: ALL (HR 2.68), ≥4 prior antitumor treatment regimens (HR 3.53), receipt of 2×10^7 CAR T cells per kg (HR 7.25), and severity of CRS (HR 3.83)	50% mild or moderate, 41% severe, 6% life-threatening, 3% fatal	Hill et al. [11] 2018
Phase I study B-ALL	53	36%	3	Days 0–30: 42% infections, mostly bacterial Days 31–180: 31% infection, mostly viral RF for infection: CRS (grade ≥ 3)	NS 5.6% fatal infections	Park et al. [3] 2018
Case series LBCL	3	33%	2	Three patients with concomitant HBV or HCV infection receiving CAR T-cell therapy HBV prophylaxis with entecavir and tenofovir No fulminant hepatitis observed	–	Strati et al. [24] 2019

Table 17.1 (continued)

Study type and hematological malignancy	n	Prior HSCT	Median prior lines of treatment	Main results	Infection severity	Reference and year of publication[a]
Retrospective 25 B-ALL, 68 LBCL, 16 MM	109	23%	NS	17% infections in the first 30 days Grade 4–5 infection and grade 3–5 CRS had higher levels of IL-6, but only CRS had also important elevations of ferritin Patients with infection had a second IL-6 peak (>1000 pg/mL) Infection predictive model based in three cytokines: IL-8, IL-1β, and IFN-γ	16% mild or moderate, 26% severe, 58% life-threatening or fatal	Luo et al. [6] 2019
Retrospective LBCL	15	NS	NS	Three patients (20%) had HBV reactivation HBeAg as a marker of infectivity No hepatitis flare	–	Yang et al. [25] 2020
Case series NS hematological malignancy	59	NS	NS	3% (2/59) invasive mold diseases: 1 *Fusarium solani* and 1 probable mucormycosis Both the patients had CRS and neutropenia	Both life-threatening	Haidar et al. [26] 2020
Retrospective 82 B-ALL, 1 LBCL	83	55%	NS	90 days before infusion: 54% infections; infection density: 1.23 per 100 days at risk Days 0–28: 40% infections; infection density: 2.23 per 100 days at risk Days 29–90: 17% infections; infection density: 0.55 per 100 days at risk RF for infection in the first 28 days: Prior HSCT (HR 2.15) and post-infusion hypogammaglobulinemia (HR 2.41)	43% mild-moderate, 45% severe, 13% life-threatening	Vora et al. [16] 2020

(continued)

Table 17.1 (continued)

Study type and hematological malignancy	n	Prior HSCT	Median prior lines of treatment	Main results	Infection severity	Reference and year of publication[a]
Retrospective LBCL	60	27%	4	101 infections (60 bacterial, 38 viral, 2 fungal, and 1 protozoal). Thirty-two during initial CAR T admission and 69 after hospital discharge (70% managed as outpatients) 1-year cumulative incidence of all infections, bacterial, viral, and fungal infections were 63.3, 57.2, 44.7%, and 4.0%, respectively RF for infection: Systemic corticosteroid (HR 2.22) RF for severe bacterial infection: Impaired performance status (HR 2.84) and infection before CAR T infusion (HR 3.98) RF for viral infection: Hypogammaglobulinemia prior to CAR T infusion (HR 5.7)	17% mild, 58% moderate, 24% severe, 1% fatal	Wudhikarn et al. [2] 2020
Retrospective 43 NHL, 17 CLL, 26 B-ALL	86	17%	4	Late events (<90 days to 1 year): 54 patients (61%) had at least 1 infection, for a total of 153 infection events Infection density: 0.55 per 100 days at risk Upper respiratory tract: 48%, lower respiratory tract: 23%	NS, but 80% outpatient, 20% admission, 5% ICU	Cordeiro et al. [10] 2020

HSCT hematopoietic stem-cell transplant, *B-ALL* acute lymphoblastic leukemia B, *CLL* chronic lymphocytic leukemia, *NHL* non-Hodgkin lymphoma, *RF* risk factors, *HR* hazard ratio, *CAR T* chimeric antigen receptor T, *CRS* cytokine release syndrome, *NS* non-specified, *LBCL* large B-cell lymphoma, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *ICU* intensive care unit

[a]Arranged chronologically

Mechanism of Action of CAR T-Cell Therapy

Adoptive T-cell therapy involves the harvesting of T-lymphocytes from a patient's or donor's blood and then stimulating the cells to grow and expand in an in vitro system. These cells are subsequently reinfused back into the patient, primed for action (Fig. 17.1). Typically, T cells act by targeting specific peptides following major histocompatibility complex restrictions. In engineered CARs the binding regions are modified, and thus, the major histocompatibility complex can be avoided, allowing the cell surface antigens to be targeted independently. As a result, the patient's own T-lymphocytes can be activated against any specific target. A lentiviral vector is commonly used to deliver the genetic material into the T-lymphocyte. CAR T constructs include an antibody-based variable region, a transmembrane domain, a CD3ζ signaling domain, and co-stimulatory domains to improve proliferation, cytokine secretion, and in vivo persistence.

The current approach in hematological malignancies uses lymphodepletion chemotherapy, followed by infusion of autologous T cells modified to express a second-generation CD19-CAR incorporating a single-chain variable fragment derived from the murine IgG1 anti-CD19 monoclonal antibody (Fig. 17.1). These infused T cells are a living therapy with the ability to persist in the host for years, potentially preventing future relapses of baseline B-cell malignancy [1].

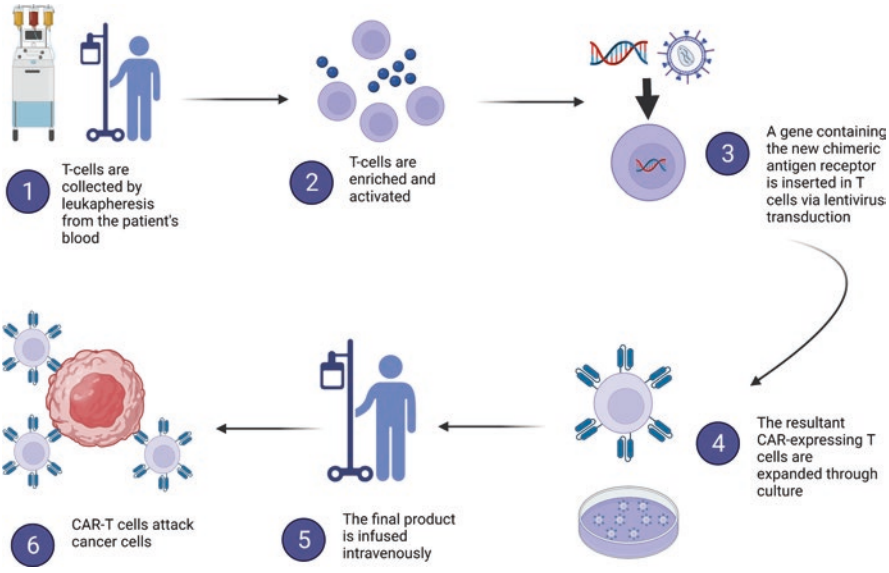

Fig. 17.1 Manufacturing CAR T cells requires several steps. T-lymphocytes are harvested from the patient by leukapheresis. After enriching and activating harvested T cells, the gene codifying the chimeric antigen receptor is inserted via transduction through a lentivirus. Genetically modified T cells are then cultured and expanded, and the final product is infused to the patient. CAR T cells react against cancer cells and can persist in the host for years

Main Toxicities Following CAR T-Cell Therapy

CRS and ICANS

CRS is a potentially life-threatening reaction mediated by the elevation of proinflammatory cytokines, including but not limited to interleukin-6 (IL-6). CRS typically coincides with CAR T-cell expansion, taking place during the first 21 days of CAR T infusion and being generally related to the tumor burden. CRS is very common with incidences ranging from 60% to 80% [2] and severe CRS (≥grade 3) presenting in 12–26% of cases [2, 3]. ICANS is the second most common adverse event related to CAR T-cell therapy and can occur separately from CRS. ICANS incidence is related to the burden of tumoral disease and the patient's age.

CRS and ICANS are commonly managed with tocilizumab (anti-interleukin-6-receptor antibody) and corticosteroids. Besides this additional immunosuppression, CRS causes endothelial damage further increasing the risk of infection [4].

CRS/ICANS can be difficult to distinguish from severe sepsis or infection. In severe sepsis, interferon (IFN)-γ is not commonly significantly elevated, although IL-6 is remarkably high [5]. This may be significantly different from the inflammatory responses of CAR T-cell-induced CRS, although strict interpretations of dynamic markers such as cytokines are challenging. Luo et al. evaluated the inflammatory characteristic signatures in CRS and infection in an attempt to differentiate them [6]. It was found that both grade 4–5 infection and grade 3–5 CRS presented with high levels of IL-6, but only CRS had significant ferritin elevation. Moreover, most patients with life-threatening or fatal infections developed a second IL-6 peak (>1000 pg/mL) immediately after the suppression of the first CRS-related IL-6 peak, with a ferritin increase of less than 50%. Other differences in cytokines were also observed such as IL8, IL-1β, and IFN-γ. After these findings, the authors propose a prediction model based on these three cytokines to help identify infections after CAR T-cell therapy. However, this work needs to be prospectively validated.

Cytopenia

The incidence of severe neutropenia following CAR T-cell infusion ranges from 20 to 80% [7, 8]. In the study by Fried et al. [9], 97% of patients developed neutropenia (72% <500 neutrophils/μL) with a median duration of 19 days, ranging from 0 to 63 days. In several patients, neutropenia was biphasic and linked to SDF-1 levels: a chemokine essential for B-cell development and for trafficking of neutrophils, as well as hematopoietic stem cells. Prolonged cytopenia during several weeks or months after CAR T infusion has been described [10].

Hypogammaglobulinemia

Due to its mechanism of action, CD19 CAR T cells also deplete normal CD19 B-cells in most patients, causing hypogammaglobulinemia. In fact, persistent B-cell aplasia is a marker of persistence of CAR T cells [8]. Additionally, most patients undergo CAR T-cell therapy due to B-cell malignancies, and a significant percentage of them have hypogammaglobulinemia prior to lymphodepletion chemotherapy. Prior IgG deficiency could be associated with an increased risk of developing hypogammaglobulinemia [10].

Different studies have shown that B-cell depletion occurs in 98% of patients within 28 days of CAR T-cell infusion, with 90-day recovery in only 20% [11]. Secondarily, around half of the patients continue to have hypogammaglobulinemia at day 30, with this percentage increasing to over 60% at later follow-up time points [2, 10]. For example, in a trial conducted in children and young adults, 83% of patients had B-cell aplasia at 6 months post-infusion [8]. Hypogammaglobulinemia seems to be more frequent and severe in patients with ALL than NHL.

Long-lived plasma cells that produce most antibodies to previously exposed pathogens may not be impacted by CD19-targeted CAR T-cell therapy due to low surface expression of CD19 [12]. Replacement therapies in patients with hypogammaglobulinemia have varied in the different studies. Immunoglobulin replacement should be considered in those patients with serum IgG levels below 400 mg/dL as well as in those with serum IgG levels between 400 and 600 mg/dL and serious or recurrent infections.

Incidence of Infection

Patients receiving CAR T-cell therapy are at high risk for infection due to underlying malignancy, prior exposure to multiple treatments (sometimes including rituximab), conditioning regimens, prolonged cytopenia, and the use of immunosuppressants to treat CRS. However, data regarding incidence of infections in these patients is scarce and may vary depending on the underlying disease and the CAR T construct.

Pivotal trials reported infections in up to 55% of patients within the first 1 to 2 years and infections of at least grade 3 severity in up to 33% of patients [8, 13–15]. Although most infections occur in the first 28 days, a heightened risk can persist for several months after CAR T infusion following cytopenia and cellular immunity dysfunction.

Hill et al. [11] divided post-CAR T infections into two different periods: early (≤28 days) and late (days 29–90). By day 28, 23% of patients had developed infections, with an infection density of 1.19 per 100 days at risk. Eighty percent of infections occurred within the first 10 days, and bacterial infections were the most

common (17%), followed by viral (8%) and fungal (3%) infections. Between days 29 and 90, 14% of patients developed infections, mainly viral (9%), followed by bacterial (6%) and fungal (2%). Infection density in this later period was 0.67 infections for every 100 days at risk. Similarly, Park et al. [3] reported 42% and 31% of patients developed infections until day 30 and from day 31 to 180, respectively. Bacterial infections predominated in the first period, while viral infections were most frequent in the later period. Vora et al. [16] reported infections in children, adolescents, and young adults receiving CAR T-cell therapy. In this study, 40% of patients acquired an infection in the first 28 days (somehow higher than in adults), mainly bacterial (most were bloodstream infections) and viral (most were respiratory viruses). Between days 29 and 90, incidence of infection was around 15%, being mostly caused by respiratory viruses. Wudhikarn et al. [2] documented all the infections in the first year following CAR T-cell therapy and found that the 1-year cumulative incidence of all infections was 63.3%, with 57.2% bacterial, 44.7% viral, and 4% fungal infections. In the first 30 days, bacterial infections were again the most frequent (68%). After the first 30 days, bacterial infections continued to be the most frequent (with similar incidence as viral infections) with most events occurring before post-infusion day 100. Finally, in the study by Cordeiro et al. [10], 61% of patients had at least one infection beyond 90 days after CAR T.

Risk Factors for Infections

Different baseline characteristics and post-CAR T-cell infusion variables have been associated with an increased risk of infection. In the study by Hill et al. [11], ALL (HR 2.68), receipt of ≥4 prior antitumor treatment regimens (HR 3.53), receipt of 2×10^7 CAR T cells per kg (HR 7.25), and more severe CRS (HR 3.83) were independent risk factors for infection. In fact, 73% of those patients experiencing CRS grade ≥ 4 also had an infection. In the study by Park et al. [3], CRS (grade ≥ 3) was the only independent risk factor for infection, being particularly associated with an increased risk of bloodstream infection (BSI—HR 2.67 for infection, HR 19.97 for BSI). In pediatric and young adult patients [16], prior hematopoietic stem cell transplant (HSCT—HR 2.15) and post-CAR T-hypogammaglobulinemia (HR 2.41) were associated with an increased infection risk in the first 28 days. In this study, severe CRS was associated with an increased risk for infection but did not reach statistical significance. Finally, from the study of Wudhikarn et al. who assessed infections until 1-year post-CAR T-cell infusion, the authors evaluated the risk factors for all infections and for severe bacterial infections, as well as viral infections [2]. They found that systemic corticosteroid use was the only independent predictor of overall infections (HR 2.22), while impaired performance status (HR 2.84) and infection before CAR T infusion (HR 3.98) were associated with severe bacterial infection. Patients with low IgG before lymphodepletion chemotherapy had almost sixfold increased risk of viral infection after CAR T cells.

The role of anti-inflammatory monoclonal antibodies (mainly tocilizumab) in the risk for infections is not clear, especially considering the relatively limited dosing of

treatment required in the CRS or ICANS setting. The experience regarding patients with autoimmune diseases requiring recurrent doses has shown these antibodies to be quite safe, although a wide range of secondary infections have been described [17]. Despite the fact that older patients and those with comorbidities seem to have a higher risk of CRS and ICANS [18], no studies have shown a clear relation with an increased risk of infection.

In summary, risk factors for infection in patients receiving CAR T-cell therapy are mainly related to the host (baseline disease and prior therapies) and procedure factors (construct and dose of CAR T cells), secondary cytopenia (mainly neutropenia), B-cell aplasia (hypogammaglobulinemia), as well as secondary inflammatory cascade (CRS and ICANS) and its immunosuppressive treatment (corticosteroids and anti-inflammatory monoclonal antibodies).

Main Types of Infection

Most studies reporting infection after CAR T-cell therapy have classified the infection severity as mild, moderate, severe, life-threatening, or fatal, following prior definitions [19]. Briefly, mild infections required no treatment. Moderate infections required only oral treatment. Severe infections required IV antimicrobial therapy or were associated with other clinical circumstances that were considered severe. Life-threatening infections were complicated by symptoms considered life-threatening and fatal infections contributed significantly to death.

Similarly to HSCT, early infections (within 28 days post-HSCT) tend to be bacterial, while late infections are typically caused by viruses and fungi [6]. For example, in the study by Park et al. [3], bacterial infections occurred at a median of 18 days (IQR, 9–29) after CAR T-cell infusion, followed by fungal infections (median 23 days; IQR, 20–29 days) and viral infections (median 48 days; IQR, 20–80 days).

It is challenging to differentiate the risk truly associated with CAR T therapy process from that related to hematological malignancy and prior treatments. For example, in the study by Vora et al. [16], 54% of patients had at least one infection 90 days prior to CAR T infusion. In fact, infection density was higher in this period pre-CAR T than in the 29–90 days period (1.23 vs 0.55 per 100 days at risk). Independently of the incidence, most infections reported after CAR T are classified as moderate or severe, with life-threatening or fatal infections ranging from 1% to 13% in the different studies [2, 6, 11, 16]. Most life-threatening infections were bacterial and mainly bloodstream infections occurring in neutropenic patients.

Two studies to date have reported the incidence and characteristics of late infections after CAR T infusion [2, 10]. Infections occurring later after CAR T-cell therapy (>90 days) are mainly mild or moderate respiratory tract infections, most commonly not requiring the admission of the patients for specific treatment. Of note, Cordeiro et al. [10] found no significant differences in late events between patients with or without ongoing complete response at the time of evaluation.

Table 17.2 displays the main type of infections described.

Table 17.2 Main types of infections described

Bacterial infections
• Most reported infections • Most episodes occurring during periods of neutropenia • Bloodstream infections are the most frequent • Most common life-threatening and fatal infections in the different studies • *Clostridioides difficile* colitis importance in patients receiving multiple antibiotics • Differentiating bacterial sepsis from CRS is challenging • CRS is an important risk factor • ICU is an additional risk factor in patients with severe CRS • Persistent hypogammaglobulinemia is a risk factor for encapsulated bacteria • High-risk for MDR bacteria in the context of prolonged and recurrent admissions, and several prior antibiotic treatments • Antibiotic prophylaxis is controversial • Anti-pneumococcal vaccination is recommended
Viral infections
• Most common infections presenting late (>90 days) after infusion • Upper and lower respiratory tract infections • Co-infection with bacteria, fungi, and other viruses is frequent • HSV and VZV reactivation can happen • SARS-CoV-2 should be ruled out at pertinent time points • Patients with chronic HBV can undergo CAR T-cell therapy under proper prophylaxis and viremia and liver function monitoring • Main risk factors for viral infections are severe CRS, prior HSCT, and hypogammaglobulinemia • Prophylaxis with acyclovir or valacyclovir is recommended in patients seropositive for HSV and VZV • Seasonal influenza vaccination and HBV in high-risk patients
Fungal infections
• Less reported, but incidence ranging from 2% to 10% • Fungemia and disseminated disease in patients with other common risk factors (prolonged hospital stay, presence of foreign bodies and instrumentalization, antibiotic selection pressure, etc.) • Invasive mold disease has been described • Risk factors for invasive mold disease in the CAR T-cell setting: Prolonged and profound neutropenia, high-dose corticosteroids, prior HSCT, several prior lines of treatment, and CRS • Antifungal prophylaxis with fluconazole is recommended in severe neutropenic patients • Anti-mold azole prophylaxis is controversial and should be considered in high-risk patients • Prophylaxis against *Pneumocystis jirovecii* with trimetroprim-sulfamethoxazole or inhaled pentamidine is recommended until CD4 count is >200/μL

CRS cytokine release syndrome, *ICU* intensive care unit, *MDR* multidrug-resistant, *HSV herpes simplex* virus, *VZV varicella zoster* virus, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *HBV* hepatitis B virus, *CAR T* chimeric antigen receptor T, *HSCT* hematopoietic stem cell transplant

Bacterial Infection

Bacterial infections are the most common infections reported in patients receiving CAR T-cell therapy, with incidences ranging from 10% to 43% and most episodes occurring during periods of neutropenia [3, 8, 11]. As these patients are heavily pretreated and have undergone several prior admissions, and likely received different antibiotic regimens, infections caused by multidrug-resistant microorganisms can arise. For example, in the study by Park et al. [3], multidrug-resistant Gram-negative bacilli, vancomycin-resistant *Enterococcus* (7/13) and *Clostridioides difficile* colitis (five cases), were common. The importance of *C. difficile* colitis in the different studies of patients receiving CAR T-cell therapy is striking, with it being the most commonly isolated agent in some studies [2]. In this setting, stewardship strategies to de-escalate and halt antibiotics, especially in those patients with CRS who do not need antibiotics, are paramount to avoiding this potentially fatal complication [20].

Neutropenic patients presenting with CRS can be indistinguishable from those presenting infection. In this setting, empirical broad-spectrum antibiotics following international neutropenic guidelines are recommended. Thorough knowledge of local epidemiology and rates of multidrug resistance are paramount. However, efforts to differentiate both complications are mandatory. IL-6 and ferritin levels together with other cytokines may be helpful, although prolonged time until having the results may be a limitation. Following the knowledge acquired from other groups of neutropenic patients, de-escalation strategies in 24–72 h can be considered [20, 21].

Viral Infections

Viral infections are the most common infection occurring late after CAR T-cell infusion. Most viral infections are upper and lower respiratory tract infections caused by respiratory viruses. Incidence varies from 6% to 28%, with a median time to presentation of 48 days post-infusion [3, 11]. Clinically, these viruses are almost indistinguishable from each other and commonly present as co-infection with bacteria, fungi, and other viruses. Patients with respiratory symptoms should undergo a chest X-ray and a multiplex PCR workup for respiratory viruses. Studies mainly conducted in allogenic HSCT patients have shown that hypogammaglobulinemia may have an impact in the prognosis of these infections. Apart from oseltamivir treatment in patients with *influenza,* many of these respiratory viruses have no optimal treatment available. Ribavirin can be considered in patients with respiratory syncytial virus, and cidofovir could be helpful in those with adenovirus, although these treatments are associated with significant toxicities.

Herpes simplex virus (HSV) and varicella-zoster virus (VZV) reactivation can happen, although the incidence in the different studies was relatively low, given that most patients received acyclovir or valacyclovir prophylaxis. There are no data on cytomegalovirus (CMV) viremia monitoring, although the risk of end-organ disease

seems relatively low. Other herpesviruses and double-stranded DNA viruses such as adenovirus and BK polyomavirus are very infrequent.

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a great health challenge, with tremendous impact on our social, economic, and health lives. Experience regarding SARS-CoV-2 infection in patients undergoing CAR T-cell therapy is scarce [22], but data from hematological patients suggest that these patients could have a worsened prognosis. In the current epidemiological context, symptoms of COVID-19 infection should be systematically evaluated. Additionally, PCR screening of SARS-CoV-2 (even in asymptomatic patients) is recommended at pertinent time points: before apheresis, lymphodepleting chemotherapy, and CAR T-cell infusion [23].

Patients with active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection have been excluded from clinical trials of CAR T-cell therapy, due to the potential risk for viral reactivation and fulminant hepatitis. Strati et al. [24] reported on three patients with relapsed/refractory diffuse large B-cell lymphoma and concomitant HBV or HCV infection receiving CAR T. No fulminant hepatitis was observed, although no patient in this study had concomitant liver cirrhosis. Later, Yang et al. [25] reported 15 patients with chronic HBV receiving CAR T cells under antiviral prophylaxis. Three patients (20%) had HBV reactivation. Two of them had HBeAg positive associated with high viral loads, but no hepatitis flare (defined as ALT level more than 100 IU/L) was observed. Following these reports, chronic hepatitis does not seem a clear contraindication for CAR T therapy in otherwise well-controlled patients. As no data exist on T-cell immune reconstitution after CAR T-cell therapy, close monitoring of HBV-DNA load and liver function, together with antiviral prophylaxis, is essential.

Fungal Infections

Rates of invasive fungal disease (IFD) after CAR T-cell therapy range from 2% to 10% in the first 100 days [3, 6, 11]. Later IFD can also occur, for example, Cordeiro et al. [10] reported four IFD in 54 patients (7%) 90 days after CAR T-cell infusion. However, these data are highly influenced by the fact that most studies performed antifungal prophylaxis with fluconazole or an echinocandin.

Impact of CAR T-cell therapy on the risk of invasive mold disease (IMD) is in discussion. In the study conducted in the Fred Hutchinson Cancer Research Center in Seattle [11], IMDs developed in 2% (3/133) of the patients: all had severe CRS and one was neutropenic with a previous HSCT. In the study from Memorial Sloan Kettering in New York [3], 7% (4/53) of patients developed IMD: all were neutropenic and three had CRS. In the study of late complications by Cordeiro et al. [10], two of the four fungal infections recorded were caused by *Aspergillus* spp. Finally, Haidar et al. [26] reported an IMD rate of 3% (2/59), with CRS and neutropenia present in both. Like prophylactic antifungal use, underlying B-cell malignancy remains a major confounder when assessing the risk for fungal infection in these patients.

Latent Infections and Screening Strategies

Patients undergoing CAR T-cell therapy should be screened for latent infections. Human immunodeficiency virus (HIV), HBV, HCV, HSV, CMV, VZV, and *Toxoplasma gondii* serologies should be obtained in all patients. Patients with history of travel to endemic countries for specific infectious diseases should be screened accordingly [27]. Screening for latent tuberculosis remains controversial, and the yield of both interferon-gamma release assays (IGRAs) and enzyme-linked immune absorbent spot (ELISpot) is diminished in these frequently lymphopenic patients. However, we recommend screening for latent tuberculosis in patients living or coming from a country with a high incidence of tuberculosis.

Prophylactic Regimens in Patients Receiving CAR T-Cell Therapy

The role of antibacterial prophylaxis in neutropenic patients is controversial as it diminishes the risk of bacterial infection but may be associated with significant selection pressure for multidrug-resistant microorganisms. Although the role of antibacterial prophylaxis in patients receiving CAR T-cell therapy is not well defined, some centers are performing prophylaxis (mainly with a fluoroquinolone) during the neutropenic phase.

In those patients with positive serologies for HSV 1/2 or VZV, prophylaxis with acyclovir or valacyclovir is endorsed for at least 6 months after CAR T-cell infusion. In patients with HBV infection, prophylaxis with entecavir, lamivudine, or tenofovir is recommended and should be maintained for at least 6 months. Additionally, serum markers of hepatitis should be closely monitored. In patients with HCV infection, specific treatment should be considered prior to CAR T therapy. CMV monitoring should be considered in patients receiving tocilizumab, high-dose corticosteroids, and those with prolonged lymphopenia.

Antifungal prophylaxis with fluconazole is recommended in patients with severe neutropenia. Anti-mold prophylaxis is controversial in this setting since the incidence seems low, and it is associated with increased costs, adverse events, and potential emergence of resistance. Some experts recommend performing a baseline workup for occult IMD prior to CAR T-cell infusion [28]. Mold-active azole prophylaxis (mainly with posaconazole) should be considered in patients with prolonged grade 4 neutropenia (>3 weeks), prior HSCT, prior IMD, several prior lines of treatment, and/or receiving high-dose corticosteroids. Similar to HSCT recipients, patients receiving CAR T-cell therapy with prior invasive fungal disease are probably at an increased risk of recurrent or new fungal infection and should be managed in a highly individualized manner [29].

Prophylaxis against *Pneumocystis jirovecii* with either trimethoprim/sulfamethoxazole or inhaled pentamidine should be considered.

Suggested prophylaxis approach is summarized in Table 17.3.

Table 17.3 Suggested prophylaxis in CAR T-cell therapy recipients

	Suggested strategy	Duration	Comments
Bacterial prophylaxis	• Consider levofloxacin	During grade IV neutropenia (<500/μL)	Bacterial prophylaxis is controversial and should follow local policies for severe neutropenic patients
Viral prophylaxis	• Acyclovir or valacyclovir in patients seropositive for HSV 1/2 and VZV • Entecavir, lamivudine or tenofovir in patients with HBV infection	At least 6 months after CAR T infusion	In patients with HBV, serum markers of hepatitis and viremia should be closely monitored CMV monitoring should be considered in patients receiving tocilizumab, high-dose corticosteroids, and prolonged lymphopenia. However, letermovir prophylaxis is not recommended
Antifungal prophylaxis	• Fluconazole • Trimethoprim-sulfamethoxazole or inhaled pentamidine for PCP • Consider anti-mold prophylaxis: – Posaconazole or isavuconazole – Echinocandin ± nebulized amphotericin B – Intravenous amphotericin B	During grade IV neutropenia (<500/μL) PCP prophylaxis: Until CD4 count is greater than 200/μL	Anti-mold prophylaxis should be considered in patients with grade IV neutropenia for >3 weeks, prior HSCT, prior IMD, several prior lines of treatment, and/or receiving high-dose corticosteroids. First choice for anti-mold prophylaxis is posaconazole. Isavuconazole can be used in case of drug–drug interactions. The other regimens are less well stablished

IV intravenous, *HSV herpes simplex* virus, *VZV varicella zoster* virus, *HBV* hepatitis B virus, *CAR T* chimeric antigen receptor T, *CMV cytomegalovirus*, *HSCT* hematopoietic stem cell transplant, *IMD* invasive mold disease

Vaccination

There exist no current international guidelines regarding vaccination in patients receiving CAR T-cell therapy. Additionally, patients receiving CD19-targeted CAR T-cell therapy are likely to have lower vaccine responses compared with healthy individuals. However, correct vaccination may still prevent infections, decrease their severity, and avoid hospitalizations. Moreover, prolonged B-cell aplasia may heighten the risk for infections caused by encapsulated bacteria.

With the immunological condition of these patients, all live and attenuated vaccines are contraindicated due to potential risk of reactivation. The main recommended vaccinations are (1) seasonal influenza; (2) anti-pneumococcal sequential vaccination: one dose of conjugated vaccine followed by one dose of polysaccharide vaccine >8 weeks later and a second dose of polysaccharide vaccine >5 years

later; and (3) HBV, particularly in high-risk populations. Once B-cell aplasia is resolved, full vaccination program can be initiated. Finally, enhancing the immunization of health-caring professionals and cohabiting relatives is essential.

Conclusions

Chimeric antigen receptor (CAR) T-cell therapy against the B-cell-specific antigen CD19 is a promising treatment for patients with relapsing/refractory B-cell malignancies. Patients receiving this treatment are at increased risk of infections due to deteriorated immune status, lymphodepletion chemotherapy, toxicities in form of CRS and ICANS, B-cell aplasia, prolonged hypogammaglobulinemia, and neutropenia. Moderate and severe infections are frequent in this setting. Bacterial infections are the most frequent, followed by viral and fungal. Risk factors for infection relate to both host and procedure factors such as neutropenia, hypogammaglobulinemia, and secondary CRS/ICANS with their respective immunosuppressive treatments including corticosteroids and anti-inflammatory monoclonal antibodies. Systematic screening, prophylactic strategies, and proper vaccination can help diminish the risk of infection.

References

1. Salter AI, Pont MJ, Riddell SR. Chimeric antigen receptor-modified T cells: CD19 and the road beyond [Internet]. Blood. American Society of Hematology; 2018 [cited 2020 Nov 10];131:2621–9. Available from: https://pubmed.ncbi.nlm.nih.gov/29728402/.
2. Wudhikarn K, Palomba ML, Pennisi M, Garcia-Recio M, Flynn JR, Devlin SM, et al. Infection during the first year in patients treated with CD19 CAR T cells for diffuse large B cell lymphoma. Blood Cancer J [Internet]. 2020 [cited 2020 Oct 27];10(8). Available from: https://pubmed.ncbi.nlm.nih.gov/32759935/.
3. Park JH, Romero FA, Taur Y, Sadelain M, Brentjens RJ, Hohl TM, 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 [Internet]. 2018 [cited 2020 Oct 25];67(4):533–40. Available from: https://pubmed.ncbi.nlm.nih.gov/29481659/.
4. Budde LE, Zaia JA. CD19 CAR-T therapy and sepsis: dancing with the devil [Internet]. Blood. American Society of Hematology; 2018 [cited 2020 Nov 9]; 131:7–8. Available from: https://pubmed.ncbi.nlm.nih.gov/29301772/.
5. Slaats J, ten Oever J, van de Veerdonk FL, Netea MG. IL-1β/IL-6/CRP and IL-18/ferritin: distinct inflammatory programs in infections [Internet]. PLoS Pathog. Public Library of Science; 2016 [cited 2020 Nov 4]; 12. Available from: https://pubmed.ncbi.nlm.nih.gov/27977798/.
6. Luo H, Wang N, Huang L, Zhou X, Jin J, Li C, et al. Inflammatory signatures for quick diagnosis of life-threatening infection during the CAR T-cell therapy. J Immunother Cancer [Internet]. 2019 [cited 2020 Oct 26];7(1). Available from: https://pubmed.ncbi.nlm.nih.gov/31640816/.
7. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380(1):45–56.

8. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med [Internet]. 2018 [cited 2020 Nov 6];378(5):439–48. Available from: https://pubmed.ncbi.nlm.nih.gov/29385370/.
9. Fried S, Avigdor A, Bielorai B, Meir A, Besser MJ, Schachter J, et al. Early and late hematologic toxicity following CD19 CAR-T cells. Bone Marrow Transplant [Internet]. 2019 Oct 1 [cited 2020 Nov 4];54(10):1643–50. Available from: https://pubmed.ncbi.nlm.nih.gov/30809033/.
10. Cordeiro A, Bezerra ED, Hirayama A V., Hill JA, Wu Q V., Voutsinas J, et al. Late events after treatment with CD19-targeted chimeric antigen receptor modified T cells. Biol Blood Marrow Transplant [Internet]. 2020 [cited 2020 Oct 26];26(1):26–33. Available from: https://pubmed.ncbi.nlm.nih.gov/31419568/.
11. Hill JA, Li D, Hay KA, Green ML, Cherian S, Chen X, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. Blood [Internet]. 2018 [cited 2020 Sep 28];131(1):121–30. Available from: https://pubmed.ncbi.nlm.nih.gov/29038338/.
12. Hill JA, Seo SK. How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies. Blood [Internet]. 2020 [cited 2020 Nov 2];136(8):925–35. Available from: https://pubmed.ncbi.nlm.nih.gov/32582924/.
13. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med [Internet]. 2017 [cited 2020 Nov 9];377(26):2531–44. Available from: https://pubmed.ncbi.nlm.nih.gov/29226797/.
14. Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. Lancet Oncol [Internet]. 2019 [cited 2020 Nov 9];20(1):31–42. Available from: https://pubmed.ncbi.nlm.nih.gov/30518502/.
15. Schuster SJ, Svoboda J, Chong EA, Nasta SD, Mato AR, Anak Ö, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. N Engl J Med [Internet]. 2017 [cited 2020 Nov 9];377(26):2545–54. Available from: https://pubmed.ncbi.nlm.nih.gov/29226764/.
16. Vora SB, Waghmare A, Englund JA, Qu P, Gardner RA, Hill JA. Infectious complications following CD19 chimeric antigen receptor T-cell therapy for children, adolescents, and young adults. Open Forum Infect Dis [Internet]. 2020 [cited 2020 Oct 27];7(5). Available from: https://pubmed.ncbi.nlm.nih.gov/32432149/.
17. Schiff MH, Kremer JM, Jahreis A, Vernon E, Isaacs JD, van Vollenhoven RF. Integrated safety in tocilizumab clinical trials. Arthritis Res Ther [Internet]. 2011 [cited 2020 Nov 9];13(5). Available from: https://pubmed.ncbi.nlm.nih.gov/21884601/.
18. Pasquini MC, Locke FL, Herrera AF, Siddiqi T, Ghobadi A, Komanduri KV, et al. Post-marketing use outcomes of an anti-CD19 chimeric antigen receptor (CAR) T cell therapy, axicabtagene ciloleucel (Axi-Cel), for the treatment of large B cell lymphoma (LBCL) in the United States (US). Blood. 2019;134:764.
19. Young J-AH, Logan BR, Wu J, Wingard JR, Weisdorf DJ, Mudrick C, et al. Infections after transplantation of bone marrow or peripheral blood stem cells from unrelated donors. Biol Blood Marrow Transplant [Internet]. 2016 [cited 2018 Aug 12];22(2):359–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26409243.
20. Puerta-Alcalde P, Cardozo C, Suárez-Lledó M, Rodríguez-Núñez O, Morata L, Fehér C, et al. Current time-to-positivity of blood cultures in febrile neutropenia: a tool to be used in stewardship de-escalation strategies. Clin Microbiol Infect. 2019;25(4):447–53.
21. Aguilar-Guisado M, Espigado I, Martín-Peña A, Gudiol C, Royo-Cebrecos C, Falantes J, et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial. Lancet Haematol. 2017;4(12):e573–83.
22. Malard F, Genthon A, Brissot E, van de Wyngaert Z, Marjanovic Z, Ikhlef S, et al. COVID-19 outcomes in patients with hematologic disease. Bone Marrow Transplant. 2020;55(11):2180–4.

23. Los-Arcos I, Iacoboni G, Aguilar-Guisado M, Alsina-Manrique L, Díaz de Heredia C, Fortuny-Guasch C, et al. Recommendations for screening, monitoring, prevention, and prophylaxis of infections in adult and pediatric patients receiving CAR T-cell therapy: a position paper [Internet]. Infection. Springer Science and Business Media Deutschland GmbH; 2020 [cited 2020 Nov 10]. Available from: https://pubmed.ncbi.nlm.nih.gov/32979154/.
24. Strati P, Nastoupil LJ, Fayad LE, Samaniego F, Adkins S, Neelapu SS. Safety of CAR T-cell therapy in patients with B-cell lymphoma and chronic hepatitis B or C virus infection [Internet]. Blood. American Society of Hematology; 2019 [cited 2020 Oct 26];133:2800–2. Available from: https://pubmed.ncbi.nlm.nih.gov/31101626/.
25. Yang C, Xie M, Zhang K, Liu H, Liang A, Young KH, et al. Risk of HBV reactivation post CD19-CAR-T cell therapy in DLBCL patients with concomitant chronic HBV infection. Leukemia [Internet]. 2020 [cited 2020 Oct 26];34(11). Available from: https://pubmed.ncbi.nlm.nih.gov/32533094/.
26. Haidar G, Dorritie K, Farah R, Bogdanovich T, Nguyen MH, Samanta P. Invasive mold infections after chimeric antigen receptor-modified t-cell therapy: a case series, review of the literature, and implications for prophylaxis. Clin Infect Dis [Internet]. 2020 [cited 2020 Oct 27];71(3):672–6. Available from: https://pubmed.ncbi.nlm.nih.gov/31756246/.
27. Sánchez-Montalvá A, Salvador F, Ruiz-Camps I, Barba P, Valcárcel D, Sulleiro E, et al. Imported disease screening prior to chemotherapy and bone marrow transplantation for oncohematological malignancies. Am J Trop Med Hyg [Internet]. 2016 [cited 2020 Nov 10];95(6):1463–8. Available from: https://pubmed.ncbi.nlm.nih.gov/27928093/.
28. Lewis RE, Kontoyiannis DP. Chimeric antigen receptor T cell immunotherapy and need for prophylaxis for invasive mold infections [published online ahead of print 12 January 2020]. Clin Infect Dis. https://doi.org/10.1093/cid/ciaa031.
29. Puerta-Alcalde P, Champlin R, Kontoyiannis DP. How I transplant a patient with a history of invasive fungal disease. Blood [Internet]. 2020 [cited 2020 Oct 19]; Available from: https://pubmed.ncbi.nlm.nih.gov/32845974/.