

Infections following CAR-T cells therapy: current state-of-the-art review and recommendations

Article history:

Received: 02.01.2020

Accepted: 12.01.2020

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The most frequent and severe complications after chimeric antigen receptor T-cells (CAR-T cells) therapy include cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), macrophage activation syndrome/hemophagocytic lymphohistiocytosis (MAS/HLH), tumor lysis syndrome (TLS), followed by B-cell aplasia and hypogammaglobulinemia. With these immunologically related events, cytokine storm and immunosuppression, there is a high risk of sepsis and infectious complications. The objective of this review was to present current knowledge on incidence, risk factors, clinical characteristics, and outcome of infections in patients following CAR-T cells therapy, as well as to present current recommendations on prophylaxis of infections after CAR-T cells therapy. Comparable to hematopoietic cell transplantation setting, specific pre- and post-CAR-T cells infusion phases can be determined as early (from 0 to +30 days), intermediate (from +31 to +100 days), and late (beyond day +100). These phases are characterized by CAR-T cells therapy-related factors and immune system defects contributing to an increased risk of infections. It is recommended that in case of active infection, CAR-T cells infusion should be delayed until infection has been successfully treated. After CAR-T cells therapy, prophylaxis should be implemented (anti-bacterial, anti-viral, anti-fungal, anti-pneumocystis), as well as treatment of neutropenia and immunoglobulin replacement should be considered. No recommendations so far can be given on revaccinations after CAR-T cells therapy.

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Keywords:

CAR-T cells, chimeric antigen receptor, infections, prophylaxis, vaccinations

Introduction

Chimeric antigen receptor T-cells (CAR-T cells) are a new cancer treatment modality for certain B-cell malignancies [1]. Adoptive immunotherapy with the use of CAR-T cells targeted against CD19-positive cells has been successful in producing durable remissions in patients with relapsed or refractory acute lymphocyte leukemia and non-Hodgkin's lymphoma (NHL) [2–6]. CAR-T cells are a form of autologous immunotherapy that already has changed the therapeutic landscape of some B-cell hematologic malignancies. Principles of CAR-T cells therapy involve initial collection of a patient's T cells by apheresis and then *ex vivo* genetic modification of the T-cells to encode a synthetic receptor that binds a specific antigen of malignant cells, followed by infusion of the modified T-cells back to the patient.

From the clinical point of view and procedures that need to be done, this therapeutic technology is somehow comparable to hematopoietic cell transplantation (HCT). It seems that both CAR-T cells and HCT as forms of cellular therapy are, and will be, of great value for patients. Although relatively excellent outcome has been shown for patients treated with CAR-T cells for relapsed or refractory B-cell malignancies, there are many issues to be solved, both in terms of remission of primary disease and complications during therapy. CAR-T cells therapy is a potentially curative treatment but is associated with life-threatening toxicities and can require long-term local follow-up evaluations and restrictions.

The most frequent and severe complications after CAR-T cells therapy include cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), macrophage activation syndrome/hemophagocytic lymphohistiocytosis (MAS/HLH), tumor lysis syndrome (TLS), followed by B cell aplasia and hypogammaglobulinemia [2–7]. With these immunologically related events, cytokine storm and immunosuppression, there is a high risk of sepsis and infectious complications.

This review was aimed to present current knowledge on incidence, risk factors, clinical characteristics, and outcome of infections in patients following CAR-T cells therapy, as well as to present current recommendations on prevention of infections after CAR-T cells therapy.

Phases post CAR-T cells therapy

With respect to predictable immunosuppression and the risk of opportunistic infections, the post-HCT period is usually divided into three phases: early (from 0 to +30 days), intermediate (from +31 to +100 days), and late (beyond day +100). These phases are characterized by immune system defects (neutropenia, lymphopenia, and hypogammaglobulinemia) and transplant-related factors (central venous access line, mucositis, and syndromes of epithelial damage) contributing to increased risk of infections. Comparable to HCT setting, specific pre- and post-CAR-T cells infusion phases can be determined (Fig. 1), although their characteristics can vary significantly.

	Day +30	Day +100	1-year
Immune system defects	Neutropenia		
	Lymphopenia		
	Hypogammaglobulinemia		
CAR-T-related factors contributing to infections	CENTRAL LINE		
	LD		
	TLS		
	CRS		
	ICANS		
High incidence infections	GN bacteria	CARV	
	GP bacteria	Encapsulated bacteria	
	CARV		
Low incidence infections	IC/IA/IM	IC/IA/IM	
		VZV	
		CMV, EBV	
		PCP	

Fig.1. Phases of predictable immune suppression and infections after CAR-T cells therapy

Risk factors for infections

Up to the end of 2019, only a few studies dedicated to infections after CAR-T cells therapy have been published [8-12]. All major studies on CAR-T cells therapy report adverse events including infectious complications.

Predisposing factors for infections after CAR-T cells therapy include primary disease (such as acute lymphoblastic leukemia (ALL) and NHL), primary disease-related immunodeficiency resulting in heavy pretreatment of patients (with most patients receiving at least four prior chemotherapy regimens, ranging up to 11 lines, and 38% of patients being post allo-HCT or auto-HCT), conditioning of lymphodepleting therapy before CAR-T cells infusion (most often regimen of cyclophosphamide+fludarabine is used, leading to cytopenia and prolonged cellular immunodeficiency), neutropenia (usual duration is one week, although 37% cytopenias are unresolved yet by day 28, and 15–35% patients develop febrile neutropenia), severe toxicities such as CRS/ICANS and their treatment with immunosuppressive drugs (corticosteroids and/or tocilizumab), B cells aplasia and hypogammaglobulinemia, and intensive care unit (ICU) admission [3, 4, 13–16].

Severity of CRS corresponds to serum cytokine profile, including interferon gamma, interleukin-2, interleukin-10, interleukin-15, and tumor necrosis factor alpha; however, no differences between patients with CRS with and without infections were found [9]. The use of tocilizumab (anti-IL-6 monoclonal antibody) in the treatment of CRS can be a potential risk factor for serious bacterial infections, nocardial infections, skin and soft tissue infections, diverticulitis, viral reactivation, and tuberculosis [3, 4, 13, 14, 15].

In the study of Hill et al., risk factors for infection after CAR-T cells infusion in univariate analysis included higher CAR-T cells dose (with two cutoff values: $2 \times 10^6/\text{kg}$ and $2 \times 10^7/\text{kg}$), more severe CRS or neurotoxicity, and ICU treatment. In multivariate analysis, the only significant risk factor for infection after CAR-T cells infusion was the severity of CRS [8].

Incidence and clinical characteristics of infections

Two US studies reported on infectious complications following CAR-T cells therapy for ALL, CLL, and NHL during Phase 1/2 studies, which followed after 53 and 133 patients had relapsed or refractory malignancies for 3 months in one study and for 6 months in another study, respectively [8, 9]. The incidence of infectious complications was 23–42% in the first month after CAR-T cells therapy and 14–31% later. These studies have shown that respectively 38% and 42% of all infections occur between 30 and 100 days after CAR-T cells infusion [8, 9]. Severe co-infections occurring with CRS include community-acquired respiratory virus (CARV) infections, including also nosocomial infections; cytomegalovirus (CMV) infections; HHV-6 infections; EBV infections; *Clostridium difficile* colitis; cholangitis; and viral encephalitis [4, 17, 18, 19].

The first infection was identified at a median of 6 (1–27) days after CAR-T cells infusion, with 80% of first infectious episodes occurring during first 10 days, including Gram-negative bacterial infections often with antimicrobial resistance. Bacterial infections were the most common (17%), followed by viral infections (8%), mainly caused by respiratory viruses. Incidence of infection between 30 and 90 days was much lower, with viral infections being the most common. During this period, B cell depletion was seen in 98% of patients

and hypogammaglobulinemia (IgG<0.4 g/L) was detected in 46% patients up to 90 days. Nevertheless, during this period, persistent disease was still present in 42% patients and neutropenia in 22% patients, what could contribute to infectious episodes. Most of the infections during the period between 0 and 90 days after CAR-T cells infusion were mild or moderate, and life-threatening or fatal infections were infrequent [8].

Infectious complications occurred in 23–42% patients during the first month after CAR-T cells infusion, including an incidence of 17% bacterial infections (bloodstream in 8–13% and bacterial site in 9–17%), 8% viral infections (respiratory virus in 6–7% and other viruses in 2–4%), and 3–6% fungal infections (yeasts 2% and mold 2–6%), although 9.5–10% of patients received antifungal prophylaxis [8, 9].

Median time to infection by organism type was 18 days (bacterial infections), 23 days (fungal infections), and 48 days (viral infections). Viral infections were the most common infection type among late infections (>30 days) in both studies. Most infections are seen within the first 30 days and are bacterial and, to a lesser extent, respiratory viral infections. Invasive fungal infections are rare and are mostly observed in ALL patients who have undergone prior allogeneic HCT. So far 10 cases of invasive mold disease (mainly invasive aspergillosis) have been described in the literature [8, 9, 11, 12].

Beyond day +100, there is still low risk of late infections. Risk factors include frequent hypogammaglobulinemia and prolonged neutropenia (in 16% of patients). Most infections in this phase are mild and treated in the outpatient setting [10].

Infection density

Infection densities were calculated as the mean number of infections for every 100 patient days [8]. Infection density was significantly higher in the first month after treatment, as compared to the later period. Infection density was 1.19 (at 0–28 days) and 0.67 (at 29–90 days) ($p=0.02$).

Analysis of severity of infections following CAR-T cells therapy showed that half of infections were mild to moderate and 41% were severe, 6% were life-threatening, and 3% were fatal infections. Overall, five patients in both studies died due to infections, four due to bacterial infections and one due to aspergillosis [8, 9].

Factors association with infection density: diagnosis of ALL, ≥ 4 prior antitumor regimens, receipt of the highest CAR-T cells dose, and the severity of CRS (grades 4–5 vs grades 1–3 vs grade 0) were associated with higher infection density within 28 days. Patients receiving a treatment regimen optimized to reduce the severity of CRS had fewer and less severe infections after CAR-T cells infusion compared with patients not receiving an optimized regimen [8]. These predictors of infection and bloodstream infection were confirmed in another study: CRS grade ≥ 3 was associated with an increased risk for any infection, with the highest risk of bacteremia [9].

With respect to infection density in the intermediate phase, mild infections required no treatment, moderate infections required oral treatment only, and severe infections required intravenous antimicrobial therapy or were associated with other clinical circumstances that were considered severe, with the exception of bacteremia due to possible skin contaminants and fever without

systemic symptoms (categorized as moderate). Life-threatening infections were complicated by symptoms considered as life-threatening [8].

Prophylaxis of infections

Before CAR-T cells therapy

The decision of treatment with a CAR-T cells therapy should be based on medical history, physical condition, and the current status of the patient. Among factors that are important in determining patient suitability for treatment are analysis of infectious profile and requirement to rule out ongoing infection. Active infections must be ruled out before starting lymphodepleting (LD) conditioning [6]. LD is contra-indicated in patients with active infection. Relative contra-indication should be estimated on individualized risk-benefit assessment. Active infection should be controlled on treatment prior to leukapheresis. Checklist of laboratory tests prior to conditioning can be useful including C-reactive protein (CRP), alanine aminotransferase (ALAT), and aspartate aminotransferase (ASPART). Infectious conditions that should be ruled out include active or latent hepatitis B or hepatitis C (test within 8 weeks of screening) or any uncontrolled infection at screening (ELIANA Kymriah, ALL study) [4]; uncontrolled active or latent hepatitis B or active hepatitis C or uncontrolled acute life-threatening bacterial, viral, or fungal infection, e.g., positive blood cultures <72 hours prior to screening (JULIET, Kymriah, DLBCL study) [15]; known history of HIV, hepatitis B (HepBsAg positive), or hepatitis C (anti-HCV); clinically significant active infection; or currently receiving IV antibiotics within 7 days of enrollment (ZUMA-1, Yescarta, NHL study) [5]. CAR-T cells infusion should be delayed until active infection has been successfully treated. Active infections should be fully treated prior to the administration of LD conditioning and the infusion of CAR-T cells products, especially given the likely cytokine-driven exacerbation of inflammatory processes.

The presence of fever should prompt blood and urine cultures, and a chest radiograph. Depending on symptoms, screening for CARV, CMV, and EBV nucleic acid testing (NAT) should be performed. Chest/abdominal CT imaging, brain MRI, and/or lumbar puncture should be considered if necessary. Empirical antimicrobial therapy based on signs and symptoms, as well as local institutional protocols, should be implemented based on the anticipation of CRS and neutropenia [6].

Early phase

At the early phase, approximately one-third of patients receiving CAR-T cells therapy have prolonged neutropenia beyond day +30 including up to 20% of patients who have neutropenia for more than 90 days. Additional risk factors for infections involve B-cell depletion and hypogammaglobulinemia [3, 4].

CAR-T cells recipients are at an increased risk of infections at the different stages of their treatment, which identifies a targeted group for prophylactic strategies. Since infections are one of the most common complications, an appropriate antimicrobial prophylaxis is required after CAR-T cells therapy, especially with respect to

antibacterial prophylaxis, as it is the most common infective problem in the early phase. Strategies established in other setting could be adopted to prevent infection after CAR-T cells therapy. Prophylactic anti-infective approach should be based on respective regimens in patients undergoing allo-HCT. The summary of European Society for Blood and Marrow Transplantation (EBMT) prophylactic anti-infective recommendations is presented in table I [6].

Viral infections seem to be of a lower significance in the early phase. So far there are no evidences that CMV, EBV, or ADV might be a significant clinical problem after CAR-T cells therapy. No data are available about the risk of HBV/HCV reactivation, neither HIV infection, as these patients are excluded from the trials. Still, for patients with a history of HBV infection, prophylaxis with tenofovir should be recommended.

Intermediate term (between day +30 and day +100) complications and management

Majority of patients face prolonged or late B-cell aplasia and hypogammaglobulinemia. Both factors might significantly contribute to infectious complications. Neutropenia, thrombocytopenia, and anemia are common at this stage; however, these conditions slowly resolve over next several months. Sometimes support with growth factor may be indicated in the early stages.

During this phase, patients should be monitored for full blood count, renal and liver biochemistry panel, LDH, ferritin, fibrinogen, CRP, quantitative immunoglobulin, and serum protein electrophoresis at every visit, as well as peripheral blood immunophenotyping for CD3/4/8/16+56/19 and CAR-T cells monitoring where commercial kits are available for routine monitoring of anti-CD19 CAR-T cells (if necessary) once a month. Polymerase chain reaction (PCR) for viral reactivation (CMV, EBV, adenovirus) in peripheral blood should be done, if clinically indicated [6].

Patients should be monitored for prolonged cytopenia, disease remission, and secondary malignancies. Prophylaxis and treatment of infection and immunoglobulin monitoring and supplementation

should be strongly considered, especially in the pediatric setting. B-cell aplasia can be used as a pharmacodynamic measure of the persistence of functional CD19-targeted T cells (CAR-T cells). The probability of relapse-free B-cell aplasia at 6 months was 73%. Continued B-cell aplasia was seen in all patients who had a sustained remission, and none of the patients with B-cell aplasia had a CD19-positive relapse [3, 4].

During this period, B-cell aplasia and hypogammaglobulinemia are two major risk factors for infectious complications. Prolonged B-cell aplasia beyond day +30 after CAR-T cells infusion is an almost universal on-target, off-tumor toxicity. It obviously results in hypogammaglobulinemia, occurs in almost all responding patients and persists even for up to one year [8]. Additionally, lymphopenia might occur [8]. B-cell aplasia can serve as a marker for monitoring presence of CD19-specific CAR-T cells activity over time.

At this phase, viral infections usually predominate including respiratory viral infections, as well as CMV viremia and pneumonia, and BK polyoma virus cystitis. Sinopulmonary infections, usually with encapsulated bacteria, might also occur. One might consider specific vaccination, but no evidence is available so far. Pediatric centers usually prefer immunoglobulin replacement following use of CAR-T cells in order to maintain IgG levels ≥ 0.4 g/L, regardless of time requirement.

Long-term follow-up

The common requirement in 2019 for new studies on CAR-T cells therapy was a long-term follow-up, even up to 15 years post CAR-T cells infusion, in order to estimate clinical condition, immune reconstitution, and remission status. Recommended tests to be performed include full blood count, biochemistry panel, quantitative immunoglobulin, and serum protein electrophoresis, as well as CAR-T cells monitoring where commercial kits are available for routine monitoring of anti-CD19 CAR-T cells (if necessary) at every visit, peripheral blood immunophenotyping for CD3/4/8/16+56/19 every second visit, and endocrine function and other standard late

Table I. Anti-infective prophylaxis after CAR-T cells therapy

Prophylaxis	Recommendation	Comment
Antibacterial	Not routine; in patients with neutropenic fever, empiric treatment with broad spectrum antibiotics is strongly recommended	Management should be based on local guidelines (e.g., with levofloxacin or ciprofloxacin)
Antiviral	Acyclovir 2 × 800 mg (in children 2 × 20 mg/kg) or valaciclovir 2 × 500 mg	Start from LD conditioning until one year post CAR-T cells therapy and/or until CD4 ⁺ count $>0.2 \times 10^9/L$
Antifungal	Not routine; however, consider if patient is neutropenic and on corticosteroids	In patients with prior allo-HCT, prior invasive aspergillosis and those receiving corticosteroids, posaconazole prophylaxis is recommended
Anti-pneumocystis	Co-trimoxazole 480 mg once daily or 960 mg three times each week	Start from LD conditioning until one year post CAR-T cells infusion and/or until CD4 ⁺ count $>0.2 \times 10^9/L$. Alternatively, pentamidine inhalation (300 mg once every month), dapsone 100 mg, or atovaquone 1500 mg once daily
Neutropenia	Not routine; however, consider if patient has severe infections in neutropenia	Avoid if patient has or had CRS (G-CSF can trigger CRS) or neurotoxicity
Immunoglobulin replacement	Routine IVIG in children (to keep >0.4 g/L) and in adults who have had infections with encapsulated organisms	Clinical evidence does not support routine use in adults following allo-HCT

General remark: it is advised to adhere to national or local guidelines or standard practice. G-CSF – granulocyte colony stimulating factor; CRS – cytokine release syndrome; LD – lymphodepleting; allo-HCT – allogeneic hematopoietic cell transplantation; CAR-T cells – chimeric antigen receptor T-cell; IVIG – intravenous immunoglobulin.

effects testing appropriate to age – yearly or as clinically indicated. Additionally, peripheral blood PCR tests for viral reactivation should be performed, when clinically indicated [6].

Vaccination issues

Live vaccines are contraindicated 6 weeks prior to CAR-T cells therapy. Since there are no data regarding revaccination, no recommendations can be given for patients after CAR-T cells therapy; however, Center for Disease Control and Prevention (CDC) suggests HCT-like protocol. Previous oncologic therapy, immunosuppressive lymphodepletion, and anti B cell properties of CAR-T cells therapy probably fully abolish effects of previous immunization. On the other hand, antigen-specific IgG antibodies may be produced by long-lived plasma cells not expressing CD19, so that preexisting antibodies may persist in CAR-T cells recipients. Thus, the existence of memory B-cell-independent, long-lived plasma cells in humans can contribute to long-lasting humoral immunity [20].

The role of vaccinations following CAR-T cells therapy is not known yet. Owing to lack of evidence, no specific recommendations can be made. This is particularly an important problem for small children who have not yet completed their mandatory immunization schedule. Therefore, this group of patients need special and close follow-up. Recent analysis has shown that humoral immunity as detected by VirScan assay to some viruses (e.g., measles) may be maintained or even recover after successful anti-CD19 CAR-T cells therapy in adults; however, there are no data available for children [21]. In general, it is recommended that if vaccines are given, response with

specific antibody should be assessed. Anticipating long-term B cell depletion, it is advised that adherence to the recommended standard national vaccination schedules should be individualized based on the history of previous vaccinations, previous infections, and laboratory assessments of humoral and cellular immunity [7].

Authors' contributions

JS – the only author.

Conflict of interest

The author was the participant of Novartis Advisory Board, has received lecture fee, and has participated in meetings organized by Gilead.

Financial support

No financial support.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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