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REVIEW ARTICLE

Infectious Complications and Preventative Strategies following Chimeric Antigen Receptor T-cells (CAR-T cells) Therapy for B-Cell Malignancies

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Abstract

Several chimeric antigen receptor T-cell constructs (CAR-T cells) are currently approved for the treatment of B-cell malignancies, including non-Hodgkin lymphoma and acute lymphoblastic leukemia. Additionally, multiple other products are being investigated and developed for other hematological malignancies and solid cancers. Patients receiving CAR-T cells are at increased risk of infectious complications that lead to increased morbidity and inferior mortality in these patients. In this review, we discuss the literature on the incidence and types of infection in patients in the early and late-phase after CAR-T cells infusion. Additionally, we summarize the current literature on prophylaxis against viral, bacterial, and fungal infections after CAR-T cells infusion and the utility of preventative and supportive measures including intravenous immunoglobulins and myeloid growth factors.

Keywords: B-cell malignancies, CAR-T cells, Infections, Prevention

1. Introduction

Six chimeric antigen receptor T-cells (CAR-T cells) products have been approved by the United States Food and drug administration (US-FDA) after demonstrating beneficial outcomes in trials [1–3]. Four of the approved products are CD19 targeting CAR T-cells used in B-cell malignancies including acute lymphoblastic leukemia and non-Hodgkin lymphoma [4]. Additionally, two BCMA-directed CAR-T products have been approved for patients with multiple myeloma. CAR-T cell approvals are expected to increase in the upcoming years given the current number of trials targeting both hematologic malignancies and solid cancers [5].

With the increasing number of patients receiving cellular therapies worldwide, identifying CAR-T cells complications is crucial to mitigate these and improve outcomes. Acute complications after CAR-T cells including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are well defined in literature [5]. However, other complications including cardiotoxicity, infectious complications, secondary malignancies and long-term effects are understudied [6–8]. Some of the delayed toxicities such as prolonged cytopenia, B-cell aplasia, and hypogammaglobulinemia not just confer an increased infection risk among CAR-T recipients but also diminish vaccine responses resulting in a significantly high infection-related mortality. Hence, there is a critical need to better understand these toxicities and mitigate them to consolidate the remission success conferred by CAR-T [9–11].

CAR-T cell therapy is expected to increase patients' susceptibility to infections due to several

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factors including lymphodepletion (LD) chemotherapy, underlying relapsed disease and immunosuppressive agents received after the infusion [12,13]. Further, increasingly sophisticated and multi-antigen targeting CARs and allowance for prophylaxis usage of immunomodulators (such as in cohort 6) will increase the cumulative dosage of corticosteroids and interleukin blockers, further compounding the infection risk [14]. Identification of patient- and treatment-related characteristics that increase the risk of subsequent infections would help risk stratify patients who may benefit from broader antimicrobial prophylaxis and timely diagnostic and therapeutic approaches.

In this review, we summarize major risk factors and infections reported in patients receiving CAR-T cells for the treatment of B-cell malignancies and the available literature on infection prevention and control.

2. Risk factors for CAR T cell associated infections

Prior lines of therapy and CAR-T cells infusion-related risk factors are thought to increase the likelihood of infections in patients receiving CAR-T cells infusion (See Table 1). Prior to receiving CAR-T cell infusion, patients usually receive multiple lines of therapy. For instance, in the ZUMA-1 trial around 70% of patients had three or more prior lines of therapy [2]. This frequently includes cytotoxic chemotherapy and hematopoietic cell transplantation which can have long-term effects on patients' immune response due to an enhanced cumulative net immunosuppression state. In one analysis, around 40% of patients with infections after CAR-T cell infusion had a prior autologous or allogeneic transplant [13].

Table 1. Summary of the risk factors identified in literature.

Pre-CAR T cell infusion
1 Impaired baseline performance status
2 Number of prior lines of treatment
3 History of recent infections (within 100 days prior to infusion)
4 Adult patients
5 Pre-infusion hypogammaglobinemia
6 History of prior allogeneic transplant
7 ANC <500 cells per $mm^{3.}$
8 Lymphodepleting chemotherapy
Post-CAR T cell infusion
1 Severe cytopenias (> Grade 3)
2 B cell aplasia
3 Hypogammaglobinemia
4 Cumulative immunomodulator exposure (tocilizumab and corticosteroid) after CAR T cell infusion

The administration of CAR-T cells requires LD chemotherapy necessitating the administration of pre-infusion LD chemotherapy. The use of LD chemotherapy can lead to immunosuppression from cytopenia, hypogammaglobulinemia, and impaired mucosal barriers. Severe cytopenias (grade 3 and above) in the first 4 weeks following the administration of LD chemotherapy are common and up to 17% of patients had persistent severe cytopenia at 3 months post-infusion [15]. Of 83 reported patients with B-ALL who received CAR T cell, pre-infusion hematopoietic cell transplant (HCT) and LD chemotherapy with a regimen other than cyclophosphamide plus fludarabine, were associated with increased infection [16].

B-cell directed CAR-T cells such as CD-19 CAR-T cells can induce hypogammaglobulinemia and long-term B-cell suppression [17]. IgG levels of <400 mg/dL by 63 days post-CAR T-cells infusion, was associated with increased infection risk [16]. Several studies have shown variable rates and duration of hypogammaglobulinemia, and its impact has been demonstrated consistently. For instance, in an analysis of 71 CLL patients who received CAR-T cell therapy, 44% of patients had hypogammaglobulinemia prior to infusion, however, 81% of patients developed or continued to have hypogammaglobulinemia post infusion [18]. The levels of IgG can vary after infusion, for example, in a review of 101 patients after receiving tisagenlecleucel or axicabtagene ciloleucel, 89% had hypogammaglobulinemia after infusion, with 57% and 13% being moderate and severe hypogammaglobulinemia, respectively [19]. Interestingly, only 23% of patients had moderate to severe hypogammaglobulinemia prior to infusion. The onset of hypogammaglobulinemia can happen as early as 6 weeks after infusion and can persist for years, indicating the relationship between CAR-T cells persistence and hypogammaglobulinemia [19].

Additionally, patients who developed post-infusion complications including CRS were reported to be at a higher risk of infection [20]. For example, *Vora* et al. [16] reviewed 83 patients who received CD-19 CAR-T cells out of whom seven patients developed grade 3 CRS from which 5 developed infections. Patients with CRS frequently receive high doses of corticosteroids and/or tocilizumab. Corticosteroids are known to predispose patients to infections, whereas tocilizumab carries a theoretical risk for infection however, clinical data is conflicting.

Other reported risk factors included CAR−T-cell dose, recent infection within the past 100 days, age >18, and infection 30 days before LD chemotherapy [13,20].

3. Incidence and types of infections

For the reasons listed above, higher incidence of infections was reported in patients after CAR-T cells for B-cell malignancies. It should be noted that the majority of studies are for patients who received CD-19 targeting CAR-T cells. The literature is heterogenic in regard to the other types of CAR-T cells used for different primary diseases. Below, we will discuss the infections according to time of onset after CAR-T cells infusion.

3.1. Early infections (first 30 days)

The incidence of infections in the early phase after CAR-T cells was variable in different studies. . For instance, Vora et al. [16] reported that 40% of the 83 ALL patients treated with CAR T-cells had an infection during the first 30 days after infusion, including four patients who had two infections during that period. Dayagi et al. [21] reported data from 88 patients receiving CD28-based CD19 CAR-T cells, 36 infections were reported in 24 patients in the first 30 days after infusion.

The type of infection varied between the studies; however, bacteremia and localized bacterial infections followed by viral infections were the most frequently reported infections during this early phase post-infusion. The ratio of bacterial infections ranged between 50 and 70% in studies [20,21]. Some studies have shown higher cumulative incidence of viral infections, for instance, Baird et al. [15] reported 19 patients (46.3%) who developed infections after receiving axicabtagene ciloleucel therapy for large B-cell lymphoma, out of which viral respiratory tract infections were the commonest. Fungal infections were less common in the first 30 days across the studies, for instance, Vora et al. [16] reported only one case of fungal infection in 83 patients in the first 4 weeks post infusion. In another study examining 280 patients who received CD19+ CAR T-cells, only 5 developed invasive fungal infection. This was despite significant early and late on-target off-tumor CAR-T toxicities and without antifungal prophylaxis [22].

The microbiological identification of organisms is reportedly around 70% of cases (Stewart and Henden 2020). Common sites include bloodstream, lung, genitourinary, soft tissues, however, bacteremia is the most encountered infection. Both gram-negative and gram-positive bacteremia were reported in patients after CAR-T cells with variable ratios. *Clostridioides difficile* colitis was also frequently reported in the literature [12]. On the other hand, most common viral infections include respiratory viruses and HSV. Cytomegalovirus, Epstein–Barr virus, and other herpesviruses are less commonly encountered after CAR-T cells [23]. Fungal infections including candida and aspergillus were reported but less frequently.

3.2. Late infections (after 30 days)

Incidence of infections decreases after the first 30 days post-infusion [16]. The majority of studies reported higher incidence of viral infections after the first 30 days. For instance, Logue et al. [24] reported the data from 85 patients with relapsed/refractory B-cell lymphoma who received axicabtagene ciloleucel, 24 bacterial infections were reported in the first 30 days, in comparison to 13 infections beyond d+30. On the other hand, 12 viral infections were reported in the first 30 days compared to 19 infections after 30 days, with the majority being upper respiratory tract infections. Higher incidence of fungal infections was reported in many studies after day+30 [15,20], but this was not consistent in all studies [23,24].

The majority of viral infections in this period are respiratory tract infections [15,24], with rhinovirus being the most common pathogen identified [12]. CMV reactivation and other herpesviruses remain uncommon in this later period. Fungal infections are the least common compared to viral and bacterial infections. Invasive fungal infections after CAR-T cells are usually reported in patients with risk factors including prolonged neutropenia and chronic steroid therapy. *Pneumocystis jirovecii* infections have rarely been reported in literature which is likely explained by the use of prophylactic agents [13,25].

Few studies have provided long-term follow-up data for infections one year after the infusion. Locke et al. [26] reported follow-up data for patients 12 months post-infusion, only two patients out of 108 patients had grade >3 infections (one patient with pulmonary infection and one patient with two episodes of bacteremia). Further studies are needed examining longer term infectious complications and their impact on remission and patients' survival.

4. Infections prevention

Patients who are planned to receive CAR-T cells should be screened for opportunistic and chronic infections including human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus, etc. Additionally, the risk of reactivation of diseases such as mycobacterium tuberculosis and strongyloides should be considered given the possibility of

corticosteroids and tocilizumab use in case of cytokine release syndrome [23].

4.1. Antimicrobial prophylaxis

As discussed previously, CAR T-cells patients are at higher risk of infectious complications and prophylaxis is recommended in this population however the guidelines are not uniform (See Table 2).

For instance, around 50% of patients received antibacterial prophylaxis in a retrospective analysis of 60 patients treated with CD-19 targeting CAR-T [20]. Several centers limit prophylaxis to patients with severe neutropenia (absolute neutrophilic count <500), however, other centers start antibacterial prophylactically post-infusion [20,27,28]. Fluoroquinolones, such as levofloxacin, are widely used, however, other options include beta-lactams [27,29].

The use of antivirals is more common compared to antibacterial prophylaxis, particularly against HSV. Wudhikarn et al. [20] reported that all patients in their analysis were on antivirals against HSV. Regimens including acyclovir or valacyclovir are generally initiated along with the lymphodepletion chemotherapy. Most guidelines recommend 3−6 months of therapy [20,27]. The use of other prophylactic antivirals against viruses such as cytomegalovirus (CMV) is not recommended for all patients, as the incidence of such infections is low after CAR-T cells infusion. Patients planned to receive CAR-T cells should be screened for opportunistic and chronic viral infections particularly Human immunodeficiency virus (HIV), hepatitis B virus (HBV) and Hepatitis C virus [23]. In case of any positive testing, initiation of treatment and referral to specialists is needed to prevent reactivation and progression of these infections. Patients with HBV are recommended to receive entecavir prior to infusion and up to 6−12 months after infusion to prevent reactivation [23].

The use of anti-fungal medications against candida is usually initiated at the onset of neutropenia and continued until ANC recovery [20,27]. The definition of neutrophilic recovery varies by institution, examples of such definitions include ANC >1000 or ANC >500 for three days [20,28]. The suggested regimen is fluconazole, with micafungin being an alternative in case of any contraindications [27]. Additionally, patients at risk of mold infections, such as patients with prolonged neutropenia and corticosteroid use, should receive antifungals with anti-mold properties such as posaconazole or voriconazole [23]. However, several institutional studies showed low rates of fungal infections which raises the question on the necessity of anti-fungal prophylaxis [22].

Patients receiving CAR-T cells should receive prophylaxis against *pneumocystis jirovecii*, preferably with trimethoprim-sulfamethoxazole or pentamidine (in cytopenic patients), alternatively, dapsone and atovaquone can be used [20,27]. The recommended duration varies in literature, but it is generally recommended to initiate at d+30 and continue prophylaxis for 3−6 months if CD4 count is higher than 200.

4.2. Supportive care

Multiple interventions have been investigated to prevent infections by addressing common infection-contributors after CAR-T cells infusion. For instance, hypogammaglobulinemia and B-cell aplasia are almost universal after receiving B-cell

Table 2. Antimicrobials used in infectious prophylaxis after CAR-T cells infusion.

Prophylaxis	First Choice[a]	Alternatives[a]	Suggested approaches
Antibacterial	Fluoroquinolones (Such as levofloxacin 500 mg PO daily).	Beta-lactams such as: Cefpodoxime 200 mg PO BID	Starts with neutropenia and until neutrophil recovery.
Antiviral (against HSV/VZV)	Acyclovir 800 mg PO BID	Valacyclovir 500 mg PO daily Famciclovir 250 mg PO BID	Starts with LD chemotherapy and continue for at least 6 months.
Antifungals	Fluconazole 200 mg PO daily If high risk of mold infection[b]: Posaconazole 300 mg PO daily or voriconazole 200 mg PO BID	Micafungin 50 mg IV q24h (if significant LFT or T-bili increase)	Starts with onset of neutropenia and continue until neutrophil recovery.
Anti-PJP pneumonia	Trimethoprim/Sulfamethoxazole 1 double-strength PO three times a week.	Inhaled Pentamidine 300 mg monthly Pentamidine 4 mg/kg IV monthly Dapsone 100 mg PO daily Atovaquone 1500 mg PO daily	Starts day +30 and continue for 3 months or more if CD4<200 cell/μL.

Abbreviations: PO: by mouth; BID: twice daily; HSV: Herpes Simplex Virus; VZV: Varicella Zoster Virus; LD: lymphodepleting chemotherapy; LFTs: Liver function tests, PJP: Pneumocystis jiroveci pneumonia.

[a] Some doses require adjustments according to renal or liver function.

[b] Patients on high dose of corticosteroids or prolonged neutropenia.

targeting CAR-T cells [17]. The data on the utility of intravenous immune globulin (IVIG) to prevent infections is inconsistent [18,20]. However, it should be noted that high-quality evidence is lacking. Thus, considering prophylactic IVIG in patients with severe hypogammaglobulinemia (IgG $\leq$400 mg/dl) or moderate hypogammaglobulinemia with recurrent infections has been suggested [30].

The use of Granulocyte Colony-Stimulating Factor (G-CSF) to shorten the duration of neutropenia, and as such decrease the risk of infections, is a widely accepted intervention in hematology. However, published data addressing the use of G-CSF for neutropenic patients post-CAR T-cells is controversial [13,31,32]. Although studies have shown that the use of G-CSF decreases the duration of neutropenia, the role of G-CSF in decreasing infections is less consistent throughout the studies [33,34]. Additionally, administering G-CSF may increase the risk and/or severity of CRS and ICANS given the increased proliferation of macrophages and monocytes that might lead to increased cytokine release [11,34,35]. A recent retrospective study including 70 patients out of which around half received G-CSF showed that patients receiving G-CSF had shorter duration of neutropenia, similar incidence in infection and CRS, however, longer CRS duration [35].

Guidance on vaccination after CAR-T cells is still generally lacking and variable depending on patients' prior and future therapies. Suggested recommendation includes receiving inactivated vaccines and live attenuated vaccines, 6 months and 1 year after infusion, respectively [23]. Vaccines should be avoided for two months after receiving IVIG.

5. Conclusion

The topic of infectious complications post CAR T-cell will become increasingly important with the increasing number of patients treated with this modality and the expected increase in the approved products and indications. The literature currently available is scarce and insufficient to appropriately inform practitioners and unify guidelines. However, we can capitalize on the currently available literature and try to treat CAR T-cell patients accordingly. High quality research should be promoted to look into this issue, ideally in a prospective setting but if logistically difficult, registry level studies using large datasets from collaborative groups can answer many questions. Ideally, we should unify efforts to adopt a stratification strategy and implement measures to mitigate the infection risk according to the strata.

Authorship contributions

AH and INM wrote the first draft of the manuscript. All authors reviewed and vouched for the accuracy of the manuscript.

Declaration of Competing Interest

None of the authors declare any relevant conflicts of interest.

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