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Post-CART-T Cell Infection: Etiology, pathogenesis, and therapeutic approaches

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ABSTRACT

Chimeric antigen receptor (CAR) T cell therapy targeting CD-19 has revolutionized the treatment of refractory B-cell malignancies. However, patients undergoing this therapy face an increased risk of infections due to compromised immune function, lymphodepleting chemotherapy, hospitalization, and therapy-related complications such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome. Patients with systemic corticosteroid use, low immunoglobulin levels, and severe CRS, are at higher risk of infection. This review article highlights the spectrum of infections encountered in CAR T cell therapy, including bacterial, viral, and fungal infections. Following consensus guidelines for vaccination and immunoglobulin replacement is recommended. Clear criteria for antibiotic usage and vaccinating household members against respiratory viruses are crucial. Understanding the risk factors, spectrum of infections, and implementing appropriate prophylactic measures are essential to optimize outcomes in patients undergoing CAR T cell therapy. By prioritizing infection prevention strategies, healthcare professionals can effectively improve patient care.

Keywords: CAR T cell therapy, infection, immunoglobulin replacement, vaccination, neutropenia, hypogammaglobulinemia.

THE CONCEPT OF CHIMERIC ANTIGEN RECEPTOR T CELL THERAPY

CD-19-targeted chimeric antigen receptor (CAR) T cell therapy is a highly efficacious treatment modality that has exhibited significant advancements in the management of patients diagnosed with refractory B-cell malignancies. By utilizing genetically engineered T cells expressing CARs specific to CD-19, a surface antigen expressed on B cells, this therapy enables precise recognition and elimination of malignant B cells. Through the activation of CAR signalling, engineered T cells are equipped with enhanced cytotoxic potential, leading to improved patient outcomes. The successful implementation of CD-19-targeted CAR T cell therapy has revolutionized the treatment landscape for patients with refractory B-cell malignancies, as evidenced by numerous studies [1,2].

RELATIONSHIP BETWEEN CAR T CELLS AND INFECTION: INSIGHTS AND IMPLICATIONS

Patients undergoing CAR T cell therapy are at increased risk of infection due to various contributing factors [3]. Initially, these patients often exhibit compromised immune function as a result of their underlying malignancy and prior cytotoxic treatments. Additionally, lymphodepleting chemotherapy administered prior to CAR T cell infusion can lead to cytopenias and potential impairment of mucosal barriers. Hospitalization in conventional wards or intensive care units (ICUs) is often necessary for these patients, who may have vascular and/or urinary catheters and may require mechanical ventilation, thereby increasing the likelihood of nosocomial infections. Moreover, CAR T cell therapy can be complicated by cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which may require treatment with interleukin-6 inhibitors and corticosteroids depending on the severity of symptoms. The use of immunosuppressors further predisposes these patients to infections [4]. Furthermore, patients undergoing CAR T cell therapy commonly experience prolonged hypogammaglobulinemia, as well as potential long-lasting neutropenia and/or lymphopenia.

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ARE THERE PATIENT SUBGROUPS WITH AN INCREASED SUSCEPTIBILITY TO INFECTION?

There are various studies aiming to identify which patients receiving CAR T-cell therapy are at higher risk of developing an infection. Patients with systemic corticosteroid use, impaired performance status, prior infection before CAR-T infusion, and low IgG levels before lymphodepletion chemotherapy were found to have a higher risk of infection [5-6]. A previous study also reported that patients with severe CRS were more prone to infection [4].

Recently, authors have published a score based on analytical parameters at the time of lymphodepletion to risk-stratify patients for infectious complications and poor survival outcomes prior to CD19 CAR-T therapy [7]. High punctuation in this score (HThigh) has been associated with an increased risk of infection. The authors propose that their score be utilized to define antibacterial prophylaxis strategies.

WHAT INFECTIONS DO THESE PATIENTS HAVE?

These patients can experience bacterial, viral, and fungal infections [3-5]. During the neutropenic phase, patients are predominantly at risk for endogenous bacterial infections associated with neutropenia or healthcare-associated bacterial infections. Fungal infections are most commonly diagnosed during this phase. It is important to highlight the high percentage of patients in this population with *Clostridium difficile* infections. This is correlated with the extensive antibiotic use in this population, as fever is commonly observed following CAR-T infusion. Establishing clear criteria for when these patients require antibiotics is of utmost importance, as well as antibiotics stewardship strategies in order to shorten treatment duration as much as possible when there is no microbiological documentation and the patient is clinically stable.

In a later stage, when patients have recovered from neutropenia, bacterial and viral infections are more frequent. Viral infections, likely related to long-term CAR-T-induced immunological dysfunction, are common. The use of vaccines in this population, and particularly vaccinating household members against respiratory viruses, may be crucial.

HOW CAN THE INFECTIONS BE PREVENTED?

The cornerstone of infection prevention in this population is antibacterial and antifungal prophylaxis during the neutropenic phase, immunoglobulin replacement in cases of severe hypogammaglobulinemia, and vaccination. These authors recommend following the vaccination and immunoglobulin replacement guidelines proposed in the most important consensus documents published to date [3,8].

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CONFLICTS OF INTEREST

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