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CART cells and infections: A deceptive association

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Over the last 10 to 15 years the treatment of patients with hematologic malignancies has seen the blossom of a large number of new agents and even new treatment strategies. Among these, chimeric antigen receptor-engineered T (CART) cells have revolutionized the therapeutic paradigm of patients with B-cell lymphoid malignancies and acute lymphoblastic leukemia (ALL).

CART cells are genetically modified T lymphocytes of the patient which are collected through an unstimulated leukapheresis. Lenti or retroviral vectors are used to introduce into T-lymphocytes a gene encoding the engineered chimeric antigen receptor.

The structure of CART cells consists of an antigen recognition domain specifically targeting the antigen CD19, a transmembrane glycoprotein expressed in over 95% of B-cell malignancies. Based on these considerations, CD19 is an attractive target for immunotherapeutic approaches. After collection, lymphocytes are engineered to produce specific chimeric antigen receptors on the cell surface and then the cells are injected back to patient.

The large majority of the data published so far refer to patients receiving CART cells for the treatment of relapsed/refractory (R/R) DLBCL. Approximately 40% of patients with DLBCL become R/R to conventional treatments and the outcome of these patients is particularly dismal with an overall response rate (ORR) of 26%.

Axi-cel and tisa-cel have demonstrated impressive clinical efficacy in R/R DLBCL. In the pivotal JULIET trial, tisa-cel led to an ORR of 52% and a progression-free survival (PFS) of 35% at 12 months [1]. In the ZUMA-1 trial, axi-cel was associated with an 83% ORR and the 5-year overall survival (OS) was 43% [2]. Very recently axi-cel as second-line therapy led to significant improvements as compared to standard of care in response rate (83% vs 50%) [3].

Infections represent a frequent CART cell related adverse event potentially being a major hurdle for the successful outcome of the patients. Several factors contribute to infection risk in patients undergoing CART cell therapy. Patients with DLBCL receive multiple therapies before CART cell leading to a cumulative immune dysfunction. In addition, the administration of lymphodepleting chemotherapy (LD) before CAR-T cell may increase the impairment of immune responses and hypogammaglobulinemia is a common finding in these patients. Cytokine-release syndrome (CRS) represents the principal complication requiring the administration of IL-6 inhibitors (tocilizumab) and/or steroids that may further increase the risk of infections. While early neutropenia might be an expected event due to the administration of LD before CART cell infusion, the mechanism underlying delayed cytopenias remains largely unclear, although this observation has been reported in 14%-31% of patients [4]. Certainly, prolonged neutropenia can predispose for significant infectious complications which indeed represent the most frequent cause of non-relapse mortality. Few studies specifically investigated the rate of infections in patients receiving CAR-T cell therapy.

Hill *et al*. evaluated 133 patients: during the first 28 days post CART infusion the cumulative incidence (CI) of bacteremia, viral infections, and invasive fungal infections (IFI) were 8%, 9% and 4% respectively [5]. Risk factors for infections were the diagnosis of acute lymphoblastic leukemia, the number of prior antitumor treatments, the dose (≥ 2 x 107/Kg) of CART cells and the presence of severe CRS. Wudhikam *et al.* showed that, among 60 patients who received CAR-T cell therapy, the CI of bacterial viral and fungal infections was 57%, 44% and 7% respectively [6]. Cordeiro *et al.* analysed late events beyond 90 days after CART cell therapy in 54 patients. In total 20% of the patients required hospital admission: the majority of the infectious complications were viral (60%) followed by bacterial (31%) and fungal (9%) infections [7].

Among viral infections, SARS-CoV-2 had a remarkable impact on the outcome of CART patients. A recent study has shown a 4.8% prevalence of COVID-19 infection among 459 patients receiving CART cell therapy [8]. Overall, 43% of the patients required admission in ICU and the COVID-19 mortality was 33%.

In conclusion, with increasing awareness that infections represent a significant threat for patients undergoing CART cell therapy, management and prevention strategies of infectious complications are eagerly required to inform clinical practice.

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