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CART Cells: A New Dawn in Cancer Immunotherapy

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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. Monoclonal antibodies (MoAb), TKI inhibitors, checkpoint inhibitors have been introduced in the daily clinical practice and contributed significantly to the improvement of the outcome of hematologic patients. Along with the development of these new drugs, cellular therapies, namely 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. CD19 is a transmembrane glycoprotein expressed at all stages of B-cell differentiation as well as in over 95% of B-cell malignancies. Based on these considerations, CD19 is an attractive target for immunotherapeutic approaches. After collection, lymphocytes are sent to a specialized laboratory where they are engineered to produce specific chimeric antigen receptors on the cell surface. After a lymphocyte depletion therapy usually based on the association of cyclophosphamide and fludarabine, CART cells are injected back to patient.

At the present, two commercial products are available (Yescarta and Kymriah) for the treatment of the following hematologic malignancies:

– relapsed or refractory (R/R) diffuse large B cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) after 2 or more lines of systemic treatment.

– Patients up to 25 years of age with B-cell acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse

The large majority of the data published so far refer to patients receiving CART cells for the treatment of 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% and only 7% of the patients achieving a complete remission (CR).

Three pivotal studies have reported the preliminary results with different CART cells constructs, showing anti-lymphoma activity in B-cell lymphoid malignancies [1-3].

The phase II ZUMA-1 trial enrolled 111 patients with DLBCL and PMBCL. Overall, 9% of the patients could not receive the cells for various reasons. The overall response rate (ORR) was 83% and 54% of the patients achieved a complete remission (CR) [1]. The Juliet trial included 147 patients with DLBCL or transformed follicular lymphoma (TFL); overall 33% of the patients were unable to receive CART cells [2]. The ORR was 59% and the rate of CR was 43%. The TRANSCEND study included patients with a wide variety of diagnoses, namely DLBCL, TFL, FL, mantle cell lymphoma and PMBCL. The preliminary analysis reported an ORR and CR of 75% and 56% respectively [3]. A recent study updated the outcome of 43 patients at 3 years after the infusion of CART cells: 48% of patients with DLBCL or PMBCL and 63% of the patients with low-grade lymphomas showed a durable remission [4].

Cytokine release syndrome (CRS) represents the most common acute toxicity of CART cells. CRS is a systemic inflammatory response following the infusion of CART cells. CRS has been described after the administration of several drugs, including antithymocyte globulin (ATG) and MoAb as well as in the setting of haploidentical stem cell transplantation [5,6].

CRS is usually considered to be due to the on-target effect derived from the action of CART cells on the specific antigen leading to the lysis of the cells and the subsequent release of several cytokines including IFN and TNF [5,6]. These cytokines in turn promote the activation of bystander's immune cells (macrophages, dendritic cells) and non-immune cells (endothelial cells) that favor the massive release of several cytokines including IL-6 holding a key role in the pathophysiology of CRS. Clinical presentation of CRS includes a variety of symptoms spanning from mild manifestations such as fever, fatigue and myalgia up to more severe cases characterized by hypotension requiring vasopressor support, vascular leakage, multi-organ failure. Respiratory symptoms are rather common and include dyspnea and cough that can progress to acute respiratory distress syndrome (ARDS) sometimes requiring mechanical ventilation. CRS usually occurs during the first 14 days after the infusion of the cells and 2-22% of the patients may present the more severe manifestations. The treatment of CRS includes the use of steroids and tocilizumab, a MoAb that binds specifically to both soluble and membrane-bound IL-6 receptors. Along CRS, the toxicity most frequently observed in patients receiving CART cells is neurotoxicity defined as Immune effector cell-associated neurotoxicity syndrome (ICANS). The incidence has been reported to vary from 12 to 55%. ICANS may manifest as confusion, headaches, encephalopathy, aphasia, lethargy, difficulty concentrating, agitation, tremor, seizures, and, rarely, cerebral edema. Deterioration in hand writing has been reported as an early predictor of neurotoxicity, and therefore, daily-writing tests is recommended to be used as a simple tool to recognize early manifestations of ICANS.

In summary, CART cells represent a novel therapeutic strategy that has been demonstrated to be able to significantly improve the outcome of patients with R/R lymphomas who otherwise have an extremely poor outcome. Certainly, longer follow-up is mandatory to define the real relevance of this approach, and all efforts to further implement the research in this field should be commended.

Conflict of Interest

Nothing to declare.

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