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Chimeric antigen-receptor (CAR) T cells: The revolution of the cell and personalized therapy for cancer

Linfocitos T modificados con receptores quiméricos antígeno-específicos (CAR-T): la revolución de la terapia celular y personalizada para el cáncer

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Adoptive cell therapy (ACT) with mature T cells expressing chimeric antigen receptors (CARs) has revolutionized the field of ACT for cancer in the last years. CARs are composed of an antigen-specific binding domain encoding the variable regions of a monoclonal antibody, linked together as a single chain antibody (scFv), fused to a transmembrane domain followed by cytoplasmic signaling domains[1]. While "first generation" CARs contained only one signaling domain (CD3 zeta chain), the technology has evolved to incorporate additional signaling domains including costimulatory molecules (i.e., CD28, 4-1BB, OX40) to further enhance the activation of T cells (second and third generations CARs). In the majority of situations, CAR T cells are autologous cells obtained from the own patient, activated ex vivo, modified with a viral vector encoding the CAR sequences and further expanded before being infused into the patient, a process that may last 10-15 days (excluding quality tests). The development of the so-called "second generation" CARS (mostly CD28 or 4-1BB) represented a critical step towards an improvement of their clinical efficacy, especially in B-cell malignancies. Thus, treatment with a single dose of CAR T cells redirected to CD19 molecule (expressed in all B cell non-Hodgkin lymphomas-B-NHL- and acute lymphoblastic leukemia-B-ALL) (CART19) resulted in dramatic clinical responses in patients with refractory B-ALL (80% complete responses, -CR-) and diffuse large B-cell lymphoma (DLBCL), the most prevalent B-NHL subtype (40% CR)[2,3]. These data, considered to be a clinical "breakthrough", led to the EMA approvement of two distinct CART19 therapies, tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta), for the treatment of patients with relapse/refractory DLBCL) (both therapies) and pediatric/young adult (up to 25 year-old) B-ALL patients (Kymriah). While these two therapies are CD19 redirected, Kymriah is 4-1BB costimulated, while costimulation is provided by CD28 molecule in Yescarta's product. If this different costimulation translates into a clinical impact on the efficacy is not known yet, although some differences in toxicity may happen.

However, this clinical success comes with a price, the development of potentially life-threatening complications: cytokine-release syndrome (CRS) and immune effector-cell neurotoxicity syndrome (ICANS)[4]. CRS is a very frequent complication (around 80% of patients) related to the in vivo expansion of T cells and cytokine production (most importantly IL-6 among others) which requires hemodynamic supportive treatment and use antibodies blocking IL-6 (i.e., tocilizumab) and/or steroids. Although most of the cases resolved, a significant proportion of the patients (up to 30%) may need treatment in an intensive care unit. A second complication, the neurotoxicity syndrome, features different grades of encephalopathy although rare cases of fatal cerebral edema have occurred. These complications have led to the development of highly-multidisciplinary units for treating CART patients, including hematologists, neurologist, intensive medicine physicians, and pharmacists, all of which makes this therapy restricted to highly-specialized hospitals.

While CART19 is the most frequently used for hematological malignancies (>200 clinical trials), CARs targeting other molecules are increasingly being developed. The B-cell Maturation Antigen (BCMA) is expressed in the majority of multiple myeloma cells, and different CARs targeting BCMA have already entered into clinical trials. Similar to what has been found with CART19, highly-refractory myeloma patients (>3 lines of previous treatment) had a response rate of 80% with almost half being CRs[5]. Such a response rate was rarely seen with other therapies on a group of patients with similar features.

Other CARs were developed to target Hodgkin lymphoma and myeloid malignancies. A CAR targeting CD30 (expressed in all Hodgkin tumor cells) was tested in two small clinical trials with some 30% CRs[6], and a clinical trial with a novel CART30 developed by our group at Hematology-Sant Pau is expected to start late this year after approval by AEMPS. In contrast to the success of CART19 for B-cell lymphoma and B-ALL, CARs for acute myeloid leukemia (AML) has been more difficult to developed, due to the absence of true tumor antigens not expressed on normal hemopoietic stem cells. CARs targeting AML tumor antigens is an

area of intensive research for patients with refractory AML, a situation that represents a true unmet medical need.

Despite clinical success with CART19 and CART BCMA, almost 50% of patients do not benefit from this therapy at this moment, either because do not initially respond or because they relapse. Thus, it is clear that there is a lot of room for improvement and, as for other therapies, knowledge of predictor's factors of response and of resistance's mechanisms is eagerly awaited. In this line, preliminary clinical data shows that in vivo persistence of CART cells may be related to improved clinical response, and the proportion of particular T cell subsets (i.e., memory T cells) in the infused product may be associated with clinical outcome. For this reason, there is an intensive research on the methods used for ex vivo T cell expansion trying to preserve those less differentiated memory T cell subsets that may enhance the antitumor effect[7]. Other areas of active research include the development of CARs that secrete cytokines that further enhance the cytotoxic effect of T cells and other immune cells (i.e., IL-12, IL-18), the so-called fourth generation or "armored" CARs. Clinical trials with these novel designs have been already started for patients with lymphoid malignancies, and it is expected to improve the response rate.

A novel concept that it is being tested recently is the use of the CART itself as a platform to secrete antitumor agents directly into the tumor microenvironment. In this sense, CARs can be designed to incorporate drugs in the format of DNA that, after protein translation, can be released upon stimulation with the tumor cells within the microenvironment, thus augmenting their efficacy while minimizing toxicities, an idea that led to the concept of CARs as "*minipharmacies*". A sounding example of this concept is the design of CARs with DNA sequences encoding antibodies either targeting tumor antigens or immunosupressive checkpoint molecules (i.e., anti-PD-1) which has been tested already in preclinical models[8].

The success of CART19 for some hematological malignancies has encouraged the application of CART for solid tumors. Despite being developed clinical trials with CARTs targeting a number of different antigens in a number of tumors, like disialoganglioside (GD2), interleukin13 receptor α2, mucin-1, human epidermal growth factor receptor 2, and several others, the efficacy was modest[9]. Several challenges must be surmounted, such efficient trafficking of CART cells to tumors and overcoming immunosuppression in order to make this therapy successful for solid tumors.

CART therapy not only has brought a new form of therapy to the field of oncohematology, but also a different way of organization to make it available. The logistics required to provide this therapy are complex, and involve not only multidisciplinary clinical care teams but also the apheresis unit and pharmacy. Blood banks and the apheresis units are involved in critical steps of the production process, such as obtaining T cells for CART production, cryopreservation and shipping to the manufacturer center, and reception of the cryopreserved CART product until infusion to the patient. All of these procedures should be implemented with the highest standards of quality since may ultimately affect the performance of the product.

The pharmacy has a very important role in the coordination of the entire process. Pharmacist play a critical role in providing access to all drugs needed for the treatment of CART complications, some of them of new indication (i.e., tocilizumab), and to create protocols for urgent delivery of these drugs at any time. On the other hand, since CART cells are medicinal products, pharmacist must guarantee traceability and validation of the cells until the moment of the administration, which may represent a new task within their responsibilities. In this regard, the extensive experience gained by the hematology and blood bank departments with cells for hematopoietic transplantation should serve as a good platform to introduce the hospital pharmacy in this "new world" of the cellular therapy.

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