A REVOLUTIONARY CAR T CELL THERAPY FOR LYMPHOID TUMOURS

Besma LAIB[1], Abir LAIB[2*], Djamel KHERRAF[2]

[1]Faculty of Nature and Life Sciences, Department of Ecology and Environment, Batna University 2, Algeria
[2]Hematology and oncology department, Nancy Hospital, France

Abstract: The development of new approaches to anti-tumour immunotherapies is booming. Advances in molecular biology and the development of various genetic manipulation tools make it possible to reprogram T lymphocytes to express a chimeric receptor including the variable part of an immunoglobulin capable of recognizing a tumor antigen associated with the expression of molecules inducing the activation of T lymphocytes. The genetically modified T cells, known as CAR (chimeric antigen receptor)-T cells, have achieved impressive clinical results in the treatment of relapsed or refractory B lymphoid haemopathies and are under development in solid tumors. T cells have powerful lytic functions and their specific targeting of tumour cells for destruction is a major challenge. These CARs, designed for the treatment of hematological malignancies, make it possible to envisage the construction of other CARs directed against solid tumors.

Keywords: tumor, immunotherapy, CAR-T CELLS, Lymphoma.

INTRODUCTION

Surgery, chemotherapy, and radiotherapy are the standard cancer treatments, However, advances in the field of immunology have led to a better understanding of how the body's own defense mechanisms can be harnessed to treat blood cancers. Research efforts in oncology focus on how the immune system can help destroy cancer cells (Batlevi *et al.,* 2016)

Cellular immunotherapy is an innovative treatment that uses the anti-cancer properties of the body's own immune cells. One of the most promising techniques is therapy with T cells carrying chimeric antigenic receptors (CAR-T cells) (Tran *et al.,* 2017). This therapy is currently in clinical trials for the treatment of cancers (Calmels *et al.,* 2018).

T cells play a crucial role in cancer prevention. Early clinical studies using unmodified T cells reported modest efficacy (Katz *et al.,* 2015), However, the development of genetic engineering techniques has allowed researchers to use non-replicating viral vectors to induce T cells to express "chimeric antigen receptors" (CARs) (Beatty *et al.,* 2014). This external intervention allows the targeting of cancer antigens associated with T cell activation (Brudno *et al.,* 2018).T cells armed with Chimeric Antigen Receptors (CAR-T cells) used in adoptive immunotherapy treatments are among the most innovative approaches for the treatment of liquid tumors (Ahmed *et al.,* 2018), CARs are recombinant receptors expressed on the surface of engineered T lymphocytes, providing them with anti-tumor properties linked to the recognition of the targeted tumor antigen, their consequent activation, and the triggering of a cytotoxic response following this recognition (Guo *et al.,* 2018)

CAR-T cells are therefore 'living drugs' since these ingested T cells will also multiply in the body upon contact with the tumor antigen, thus increasing their capacity to destroy cancer cells expressing the targeted protein and allowing active surveillance in case of cancer recurrence (Zhai *et al.,* 2018). Most clinical studies have been performed with autologous CAR-T cells targeting the CD19 antigen, an antigen expressed by several types of B-cell leukemia, and have shown unprecedented and very encouraging complete remission rates. The medical community is unanimous that this is a paradigm shift in the way cancer is treated, and we are witnessing the beginning of a major revolution in the field of gene and cell therapy (Tipton *et al.,* 2016).

METHODOLOGY
List of abbreviations
BCMA : B-Cell Maturation Antigen
CAR : « Chimeric Antigen Receptor », récepteur chimérique à l'antigène
LAL : Acute Lymphoblastic Leukaemia
TCR : T-cell receptor
CRS : cytokine release syndrome or cytokine storm
TNF : tumour necrosis factor
CSH : hematopoietic stem cell
OS : overall survivala

Clinical trials and methodology followed

This work represents a survey in the field of lymphoma and solid cancer treatment as well as the implementation of CAR T-cell therapy, A series of studies is being carried out with the aim of issuing practical recommendations for the management of patients undergoing treatment with CAR T-cells.

Clinical trials

CAR-T therapy continues to be offered to patients in clinical trials. Research protocols vary. Depending on the clinical trial, the treatment may be administered in a hospital setting or in an intensive outpatient treatment center with health professionals experienced in administering cellular immunotherapy, Patients may have to stay at the treatment center or may not be able to leave the center before, during or after treatment. In some protocols, patients are required to have a family caregiver before being admitted to the study (Zeltsman *et al.,* 2017).

*****Correspondence**: *Abir Laib, Hematology and oncology department, Nancy hospital, France, email: laib.abir@gmail.com*

T cell collection from a patient

T cells are collected by apheresis, a technique in which the patient's blood is removed to extract one or more components (such as plasma, platelets, or white blood cells). The blood is then reinjected into the patient (Rafiq *et al.,* 2017).

Genetic manipulation of T cells in the laboratory

The T cells are sent to a laboratory where they are genetically modified with deoxyribonucleic acid (DNA) to produce chimeric antigenic surface receptors, These receptors are proteins that allow T cells to recognize an antigen on target cells (Brown *et al.,* 2016).

Multiplying the number of CAR-T cells

The number of genetically modified T-cells is "increased" by multiplying them in the laboratory. When there are sufficient numbers, the CAR-T cells are frozen and sent to the hospital or center where the patient is treated (Hartmann *et al.,* 2017).

Thawing of CAR-T cells in the hospital and injection into the patient

Many patients receive a short course of chemotherapy with one or more agents (lymphodepletion) to reduce the number of normal T cells in the body. This frees up space for CAR-T cells before patients receive the infusion, After being injected into the patient's bloodstream, the CAR-T cells will multiply. They will form an 'army' that will patrol for cells expressing the target antigen and attack them (Feldmann *et al.,* 2017).

RESULTS AND DISCUSSION
Main results of the clinical trials

The choice of target is essential to achieve the best efficacy with acceptable toxicity. Ideally, the target should be uniformly, significantly, and selectively expressed on tumor cells. This criterion is not the only determinant of the efficacy of CAR-T cells; the heterogeneity of antigenic expression on the different tumor clones of certain tumors and clonal selection can contribute to the escape of CAR-T cells. Conversely, the choice of the target will condition the toxicity of CAR-T cells by the induction of an "on-target/off-tumor" effect which is linked to the destruction of healthy tissues by CAR-T cells in the case of shared expression of the antigenic target outside the tumor tissue. Many target antigens have been selected for hematological malignances and solid tumors (Fesnak *et al.,* 2017).

Table 1.

Selection of the CAR target

Tumour	Antigenic target of RACs
Malignant haemopathies	
LAL B	CD19, CD20, CD22, CD23
LNH B, LLC	CD19, CD20, CD22, CD23
Hodgkin	CD 30
Myélome	BCMA, CD138
Hémopathies	CD5, CD7
Solid tumours	
Pancreas	MSLN
Prostate	PSMA
Breast	MSLN, HER2
Ovary	A- folate receptor
Stomach	HER 2
Liver	GPC3
Metastatic colon	HER2

The most studied targets to date are listed in Table 1. In one-hematology, the success of CAR-T cells directed against CD19 in B lymphoid haemopathies is linked to the usual expression of this target by tumor B clones, whereas CD19 is not expressed on the surface of hematopoietic stem cells. However, it is expressed by non-tumor B cells, and the persistence of CAR-T cells is associated with B aplasia and profound hypogammaglobulinemia (Mikkilineni *et al.,* 2017).

Other targets are being developed in mature lymphoid haemopathies: CD20, CD22, and CD23 for lymphoma/chronic lymphocytic leukemia (which will have the same consequences as the CD19 target on B lymphopoiesis). CD30 is a known target for certain T-cell lymphomas and in Hodgkin's disease: 4 clinical trials with CARs targeting CD30 for these haemopathies are currently open worldwide (China and USA). Of the potential targets in myeloma, BCMA and SLAM-7 are the ones receiving the most attention (Bagley *et al.,* 2018).

BCMA is a member of the TNF family, uniformly expressed on tumor plasma cells. Several clinical trials injecting anti-BCMA CAR-T cells have suggested its remarkable efficacy in multi-treated myeloma with acceptable toxicity. In myeloid haemopathies, it is very difficult to find targets expressed by leukemic cells that spare hematopoietic stem cells. Most of the targets such as CD123, CD33, and FLT3, which are being developed in clinical trials, target stem cells and will induce prolonged bone marrow aplasia. With conventional CAR-Ts, these strategies should be considered as approaches to achieve remission before HSC allograft (bridge to transplant concept) (Morgan *et al.,* 2010).

In the field of solid tumors, the first successful experiences from the clinical development of CAR-Ts

targeted HER2. In the first study with a third-generation CAR with signaling modules for CD3, CD28, and 41BB and high affinity, limiting lung toxicity forced the termination of development. The use of a second-generation CAR with lower affinity for HER2 (signaling modules for CD3 and CD28) (Fesnak *et al.,* 2017). , on the other hand, has enabled the treatment of patients with solid cancers expressing HER2 with good safety and clinical efficacy. We note some reported efficacy of CAR-T cells, targeting EGF receptor variant III (EGFRvIII) or HER2, in a small series of glioblastoma patients, suggesting the ability of genetically modified T cells to access the central nervous system. In parallel, trials with intra-tumoral injection of anti-IL-13R CAR-T cells have been reported with promising results (Milone *et al.,* 2018).

Table 2.

Results of clinical trials for the registration of tisagenlecleucel and idecabtagene vicleucel

Number of patients	product	Diseases treated	Targeted antigen	Frequency of occurrence of SRC %	Frequency of occurrence of neurological toxicities %	Overall response rate %	Data on survival
55	Tisagenlecleucel	LLA	CD19	70	30	81	1-year OS rate of 76%.
28	Idécabtagène vicleucel	multiple myeloma	BCMA	18	11	64	Median duration of OS of 18 months

The main published clinical trials are evaluating CAR-T cells targeting the CD19 antigen, expressed on the surface of B cells almost throughout their differentiation. Targeted diseases include acute lymphoblastic leukemia (ALL) (Maude *et al.,* 2018), malignant non-Hodgkin's lymphoma (Turtle *et al.,*2016), and chronic lymphocytic leukemia (CLL) (Turtle *et al.,*2017), all of which are at advanced, relapsed or refractory stages. The response rate is higher for ALL than for mature B lymphoid haemopathies.

Table 2 summarises the key data from the two clinical trials that registered tisagenlecleucel and Idécabtagène vicleucel in two indications: relapsed or refractory pediatric and young adult ALL and relapsed or refractory non-Hodgkin's B lymphoma, A significant proportion of CLL is refractory to CAR-T Cells therapy; the reasons for this resistance are gradually being elucidated (Fraietta *et al.,*2018) Some one-off successes have been reported in patients with advanced multiple myeloma, even though CD19 expression on normal and tumor plasma cells is low or undetectable.

Relapses occur in a significant proportion of treated patients. Mechanisms of relapse include the disappearance (or lack of persistence) of CAR-T cells - a particularly relevant concern for allogeneic CAR-T cells - and raise the question of the need to consolidate remission, for example by continuing the treatment strategy with allogeneic hematopoietic cell transplantation (Garfall *et al.,* 2016). Loss of CD19 expression in leukemia or lymphoma cells is another mechanism of tumor escape (Sotillo *et al.,* 2015).

For patients with multiple myeloma, the most recent clinical developments target the membrane antigen BCMA but other potential targets are being explored (Brudno *et al.,* 2018). The clinical results are convincing for this disease where there is a lack of potentially curative treatments, even after the administration of combinations of the most recently marketed drugs (Ali *et al.,* 2016). Toxicity seems acceptable for this fragile patient population. In this disease, CAR-T cells could meet a medical need that has not yet been met. Two major difficulties have to be solved, which are the accessibility of tumor cells within the stroma and the immunosuppressive properties of the tumor microenvironment (Gogishvili *et al.,* 2017).

Toxicity of CAR T-cell treatments

According to our clinical trials, the three most clinically significant complications are:

Tumour lysis syndrome (TLS) and anaphylactic reactions

LTS may be due either to conditioning chemotherapy prior to CAR T-cell administration or to direct CAR T-cell toxicity. Anaphylactic reactions may occur after the 2nd or 3rd CAR T-cell injection (Gust *et al.,* 2018).

Cytokine Release Syndrome (CRS)

This is the most common complication that can occur after CAR T-cell therapy. The incidence varies between 50 and 100%, including 2-50% of severe forms, There is a relationship between the occurrence of CRS and the degree of activation and expansion of CAR T-cells after injection. Several cytokines are involved, including IL-6, and IL-10, whose serum levels are elevated, and there is also an increase in CRP and ferritin (Frey *et al.,* 2018). SRC can occur between 1 and 14 days after cell infusion and last between 1 and 10 days. The first clinical manifestation is fever, which is often very high (41°C). Other symptoms are myalgias, fatigue, anorexia, capillary leakage, hypotension, and/or hypoxia. It can lead to the death of the patient if it is not controlled quickly. The risk factors that have been found are the tumor burden (Neelapu *et al.,* 2018), the dose of cells infused, the type of CAR construct, the nature of the target expressed on the surface of the tumor cells, the type of chemotherapy administered as conditioning for lymphodepletion. The severity of CRS correlates with

CRP and IL-6 levels but also increases with infectious disease (Brudno *et al.,* 2016). Treatment for severe cases, in addition to symptomatic management, involves tocilizumab or atlizumab, monoclonal antibodies to the del-IL-6 receptor, and steroids. It is important to be very vigilant and to ensure immediate management of the SRC, including consideration of risk factors, to prevent severe cases (Porter *et al.,* 2018).

Neurological toxicity

The main manifestations of neurological toxicity observed in trials with anti-CD19 CAR T-cells are signs of encephalopathy or seizures. In addition, patients may present with headaches, aphasia, apraxia, and facial paralysis. The incidence varies between 12 and 55% according to the studies (Locke *et al.,* 2018).

The mechanism of this neurological toxicity is not fully understood. CAR T-cells can enter the cerebrospinal fluid, and it is hypothesized that this is due to the direct toxicity of CAR T-cells or inflammatory cytokines produced by CAR T-cells in the central nervous system and the blood-brain barrier. A new hypothesis puts forward an attack on the endothelial cells of the blood-brain barrier as well as on the pericytes, mural cells located at the basal membrane of the capillary endothelium (Lee *et al.,* 2014).

Neurological toxicity may accompany SRC or occur independently and with delay. There is no effective treatment, tocilizumab and corticosteroids are not as effective as for treating SRC. Complete resolution of neurological symptoms is reported in many cases (Schuster *et al.,* 2017).

Approaches to enhance CAR-T persistence and activity

Given the importance of TCM or TSCM memory cells to ensure the long-term persistence of injected CAR-Ts, some authors have proposed transducing selected TSCMs and TCMs. Virus-specific memory T cells such as EBV and CMV (characterized by long-term persistence) transduced with the CAR receptor of interest have also been used (Pan *et al.,* 2018). Other teams have modified CAR-Ts to secrete cytokines that promote their survival or activity. It has been shown that a CAR-T secreting IL-12 (constitutively or after activation) has an increased cytotoxic activity while inducing a Th1 repolarisation attracting endogenous T cells and cells of the innate immunity. A recent publication shows that IL-18-secreting CAR-T exhibits increased expansion and persistence (Raj *et al.,* 2018), Similarly, the expression of IL-15 is likely to promote the proliferation and persistence of CAR-T.

CONCLUSION

After years of proof of concept supporting the value of cancer immunotherapy, synthetic biology is ushering in a golden era in which adoptive T-cell therapy has a place of choice. T cells are "bombs" capable of rapidly lysing large tumor masses. The advantage of CARs lies in their ability to specifically recognize a tumor cell.CAR-T cells have revolutionized the world of anti-tumor immunotherapy.

CAR-T cells target antigens overexpressed almost exclusively by tumor hepatocytes, resulting in a specific cytotoxic effect, and therefore less toxicity and protection of healthy tissues, associated with the inhibition of tumor proliferation. These results provide a comprehensive description of the anti-tumor activity of CAR-T. However, the wider use of this type of therapeutic approach requires further analysis of CAR-T cell toxicity and side effects. Nevertheless, this study is interesting because it overcomes some of the obstacles to the use of CAR-T cells in solid tumors and provides scientific proof of the efficacy of this type of approach, which opens up a promising therapeutic field for the treatment of cancers.

AUTHORS CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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