

CAR T-cell Technology Basics and Clinical Application in Non-Hodgkin Lymphoma

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Abstract: Despite the progress made in the treatment of Non-Hodgkin Lymphoma (NHL), relapsed and refractory patients fail to be cured with conventional immuno-chemotherapy even in the era of type I and II anti-CD20. Since B-cell and T-cell lymphomas are antigen presenting cells, they represent good candidate for the chimeric antigen receptor (CAR). CAR showed to be a promising approach in several solid malignancies, however, experience in NHL is still poor despite the daily increasing understanding of the biologic mechanism underlying the development of such diseases. CAR itself faces several challenges such as improving selectivity against certain cells as well as overcoming the inhibitory cytokines secreted from the cancer stroma and the microenvironment as well. In this study, we will shed light on the biologic and practical designation of CAR, results in some malignancies including NHL and the way to improve efficacy in future.

Keywords: CAR, T-Cell, Non-Hodgkin lymphoma, Clinical application

1. INTRODUCTION

One of the most important advances in cancer treatment during the last 10 years is the emergent role of immunotherapy which employs the cell mediated immunity producing an anti-tumor effect (1). Immune checkpoint inhibitors, play a major role as a new therapeutic approach in cancer therapy with a huge progress achieved in several malignancies especially in metastatic Melanoma by using two new molecules: ipilimumab which blocks the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and nivolumab which blocks in turn the programmed cell death 1 receptor (PD-1) resulting in notable improvement of both progression free and overall survival rates (2,3). Immunotherapy does not target tumor cells it selves, however, it targets the microenvironment and improves the function of the immune system (4). Cancer immune-editing theory is an extrinsic suppressive mechanism which is activated after the cancer cell transformation occurs as a consequence of intrinsic suppression failure. This mechanism is composed of three stages: Elimination, Equilibrium and Escape (3 Es). The Elimination phase: in this phase, the organism can identify tumor cells by the immune system because of cytokines secreted by those newly formed cells which recruit immune cells like natural killers, macrophages,

dendretic cells and $\gamma\delta$ T-cells. At this stage the immune system is able to eliminate the newly formed cells, however, if some cells survive, then the next phase is activated. The Equilibrium: the immune system applies pressure on the survived cells which may last for 20 years before the clinical detection of tumor takes place. The Escape phase: in this phase, the genetic instability allows the newly completely transformed cells to resist the immune system and survive leading to a cancer formation (5). In 1980, Rosenberg was the first to describe the capability of expanded autologous lymphocyte to destroy tumor cells in culture (6), this finding led to the first steps made in Adoptive T-Cell Therapy (ACT) understanding. Several years later, Rosenberg et al showed that a subpopulation of tumor infiltrating lymphocytes (TIL) are capable of eliminating cancer cells in advanced and metastatic cancers (7). Those tumor infiltrating cells, isolated from the tumor, expanded and activated in vitro then re-infused back to the patient showed good response (8). TIL was firstly used to treat Cytomegalovirus and Epstein virus then developed to treat renal cell carcinoma, however, the efficacy was disappointing with a poor complete response of 7% (9). To better developing an effective immunotherapy, the patient's own T-cells

should be directed to a specific antigen by engineering them to express a modified T-Cell Receptor (TCR) or Chimeric Antigen Receptor (CAR).

In this review, we will concentrate on the basics of CAR development and the clinical application in Non-Hodgkin Lymphoma (NHL) which arise from a clonal expansion of both B and T cells as well as Natural killer cells. Although malignant cells express its own genetic and phenotypic markers, it also retain some of phenotypic markers of the original tissue they originate from (10).

2. DESIGNATION OF CAR T-CELLS

Autologous T-cells are isolated by means of leukapheresis then the desired genes are transfected by vectors (retroviruses or plasmids). The next step is expanding the cells *ex vivo* and transferred to the patient after

giving a high dose chemotherapy. CARs are able to recognize unprocessed antigens expressed on tumor cells without the engagement of MHC (11). The mechanism by which CARs eliminate tumor cells by redirecting both CD4 and CD8 lymphocyte leads to cytolysis through several mediators including perforin, granzyme exocytosis as well as death receptor signaling via Fas/Fas-ligand and TNF/TNF-receptor (12).

The antigen binding domain and the transmembrane domain are separated by a spacer. The most important and more stable receptor in the transmembrane domain is the CD28 which is linked to an intracellular moiety CD3 ζ which triggers the first signal of T-cell activation. In order to increase cytokines secretion, a second signal through the interaction between CD28 or 4-1BB is delivered (13) as illustrated in figure (1).

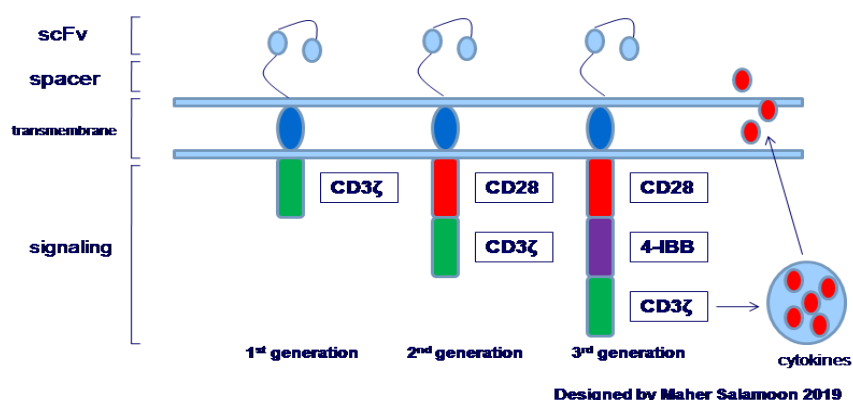


Figure1: represents the structure of CAR with an extracellular domain consists of scFv from a monoclonal antibody responsible for cancer cell recognition linked to the intracellular signaling domain. The 1st generation Car signals through CD3 ζ only, while the 2nd generation using CD3 ζ as well as either CD28 or 4-1BB. The 3rd generation as illustrated, signals through the hetero-dimer of CD28/4-1BB as well as CD3 ζ . This combination leads to secretion of pro-inflammatory cytokines leading to target cell lysis.

3. BASICS OF GENETIC ENGINEERING OF T-CELLS

3.1. Transfection Through Viruses

Viral transduction is the best way to transmit genes of interest into the T-cells using several kinds of retrovirus, lentivirus and adenovirus. Among the viruses used in gene transfer, retroviruses are still the preferred mean because they can incorporate in the target genome, confer good genomic stability with a minimal immunogenicity. Other important characteristics of the retroviral genome is that the whole viral genome can be replaced by the transgene of interest, further, once the transgene is inserted, it will be permanently incorporated in host genome. In order to form a CAR vector,

essential genes such as *gag*, *pol* and *env* are removed from the viral genome backbone delivered in *trans* in helper plasmid and a CAR transgene is inserted instead of them. A cell line is prepared and transfected with both CAR transgene and helper plasmid. Stimulated T-cells, OCT3/CD28 and retroviral particles are incubated and once the virion core is released into the cytosol and transported by the microtubules to the nucleus leading to the production of T-cells with high CAR expression (14,15).

3.2. Transposons

It is a bi-component vector system composed of the transposons which is a plasmid carrying the CAR and the transposase carried on another

plasmid which acts on the inverted terminal repeats conferring a stability of the transgene integration. Once the transposons and the transposase are electroporated into the T-cells, the CARs are expressed on the T-cells surface. This technique is less toxic, more effective and cost effective when compared with other techniques (16).

3.3. CRISPR/Cas9

One of the most important revolutionary technology in genetic editing was the CRISPR/Cas9 which can target any genomic region through a short RNA guide acting as an endonuclease which can be transfected by several means in the form of Cas9 protein/gRNA ribonucleoprotein (17).

3.4. Non-Viral Transfer Methods

The first use of mRNA in genetic engineering was first described by Malone et al 1989 using liposome transfection method (18). Zhao et al described in 2006 the transfer of TCR genes into the primary T-cells via electroporation of mRNA (19). However, mRNA transfection technique should be improved because of several challenges such as: susceptibility to degradation, sensitivity, negative charge and the insufficient translation in the host cell.

3.5. Aggressive B-Cell Non-Hodgkin Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-hodgkin lymphoma (20) treated with a combination of type I anti-CD20 plus chemotherapy (21). Most of treated cases are curable with the first line combination chemo-immunotherapy, however, 10-15% show a primary refractory disease (20). In those refractory patients, another second line of immune-chemotherapy is delivered followed by autologous peripheral stem cell transplantation (ASCT) with a variable outcome, where two thirds of patients do not show a complete remission as a response to the salvage treatment, therefore, they are not eligible for autologous stem cell transplantation (22). Therefore, patients who are refractory and ineligible for (ASCT) need more investigation to reach a curable approach, that is why, axicabtagene ciloleucel was investigated in the ZUMA-1 clinical trial.

4. WHICH LYMPHOMA ANTIGEN TO TARGET BY CAR?

CAR T-cell can target and eliminate malignant B-cells expressing (CD19, CD20 and CD22),

however, those cells are also expressed on the normal counterpart of lymphoid tissue leading to B-cell ablation. Therefore, it would be of value to target the more restricted lineage-associated antigen such as B cell maturation antigen (BCMA) (30). T cell expressing antigen could be targeted as well by CAR T-cell, however, the T cell function is less amenable to replacement therapies than that of B-cells except in those lymphomas with high expression of CD30. Targeting only one antigen can lead to subsequent immune escape and resistance, therefore, expressing multiple CARs in T cell is more safe leading to the generation of T cells able to target a unique antigen that is only present on the malignant cell or its associated stroma (31). CD19 is expressed in all stages of B cell maturation and differentiation which is also highly maintained on transformed malignant cells (32) such as non-hodgkin lymphoma and chronic lymphoblastic leukemia.

4.1. Axicabtagene Ciloleucel Delivery

4.1.1. Conditioning and Infusion

In order to infuse CAR T-cell, a conditioning chemotherapy is given over 3 days. This step along with lympho-depletion determine the efficacy of CAR T-cell. Conditioning aims at removal of cellular sinks of pro-survival and T-cell activating cytokines such as IL-15 which lead to a creation of a suitable environment for CAR T-cell expansion and survival (23). Other benefits of conditioning is decreasing immunosuppressive regulatory T-cell and activating the antigen presenting cells (24). Many regimens were studied as conditioning before CAR T-cell infusion, however, no definitive regimen was found to create the ideal environment for CAR T-cell engraftment. It was postulated by the national cancer institute that fludarabine and cyclophosphamide may form a good combination as a conditioning before CAR infusion (25). It was found that anti-CD19 CAR T-cell therapy after a low dose of Cyclophosphamide 300-500mg/m² plus Fludarabine 30mg/m² for 3 days resulted in good response in aggressive lymphoma when compared with high-dose regimens (25). The former combination leads to a better in vivo expansion of CAR and higher response rates when compared with cyclophosphamide alone (26). IL-15 elevation may lead to the Cytokine Release Syndrome (CRS), however, it is correlated with CAR expansion and increased remission (23). Once the conditioning regimen is delivered, the Car T-cell is thawed at the bed

side and infused as in patient basis, then the patient is kept under careful supervision (27).

The NCI reported a case series of 22 patients with aggressive lymphoma of which 19 with DLBCL, 2 with transformed follicular lymphoma and 1 with mantle cell, prepared with low dose Fludarabine 30mg/m² and Cyclophosphamide 300mg/m² given daily on days -5, -4 and -3, then CAR T-cell is delivered at a dose of 2000000 cells per kg of body weight on day 0. The overall response rate was 73% with 55% showed a complete response. The most frequent documented adverse events were hypotension seen in 4 out 22 patients and neurologic side effects such as encephalopathy and confusion (23). In refractory aggressive NHL, Locke et al, reported rapid and durable response rates using axicabtagene ciloleucel in the phase-I portion of ZUMA-1 trial with an overall response rate of 71% and a complete response rate of 57%, however the number of included patients was modest (7 patients) (28). Those former results were consistent with that reported from the 101-patients primary phase-2 of ZUMA-1 showing an overall response rate of 82% including a complete response rate of 54% in those with DLBCL (29).

4.1.2. Targeting CD20

One of the few studies employed the first generation of CAR targeting CD20 included 7 patients with follicular lymphoma and mantle lymphoma. After a proper preparation and manipulation, T cells persisted in vivo for up to 9 weeks. Those patients were also received a subcutaneous low dose of IL-2 with 2 patients got a complete response, one showed partial response and the remaining four showed a stable disease (33). Two patients with refractory DLBCL were treated with cloned CD8+ T-cells expressing first generation CD20-CAR after an autologous stem cell transplantation, however, the procedure failed to give any kind of response. Transfected T cells were detected by PCR in peripheral blood for less than 7 days (34).

4.1.3. Targeting CD30

CD30 is highly expressed in almost all Hodgkin lymphoma (HD) subtypes and on some non-hodgkin lymphoma (NHL). CD30 is targeted by monoclonal antibodies, however, the duration of response is short, therefore, 9 patients with HD and NHL/ EBV+ disease were previously exposed to anti-CD30 (Brentoximab), treated with CAR with a peak after 1 week of infusion.

Among the eight evaluable patients, four patients showed a stable disease, one had a complete response, another one with partial response while the remaining three had disease progression (35).

4.1.4. Toxicity Profile in NHL

Safety is a head-line in the context of treatment with CAR because several life threatening complications can take place especially the Cytokine Release Syndrome (CRS) which is attributed to the rapid activation of infused CARs and the subsequent release of pro-inflammatory cytokines like TNF- α and IL-6 (36). The severity of this syndrome can be reduced by modifying T-cell dose escalation and by blocking the effects of both TNF- α and IL-6. Longer duration of toxicity is attributed to the indirect destruction of tissues and stroma expressing the target antigens leading to hypogammaglobulinemia as a result of B-cell aplasia in some patients (36). Gene delivery itself can be toxic through insertional mutagenesis induced by retroviral vectors that may lead to T-cell leukemia because of uncontrolled proliferation of T-lymphocytes (37). Since CARs prone to expand overtime, it is postulated that the body will be exposed to a cumulative toxicity, that is why it is thought to create CARs with suicide genes activated in case of toxicity. Toxicity can also be reverted by using a caspase-9 similar molecule to promote apoptosis in CARs.

5. HOW TO INCREASE CAR EFFICACY?

Malignant cells especially lymphoma cells along with its stroma and microenvironment develop means of resistance through secreting of immunosuppressive cytokines, recruiting immunosuppressive cells, dendritic cell maturation inhibition and expressing suppressive molecules on their surface (38). Several approaches were postulated in order to increase CAR efficacy through dealing with the inhibitory mechanisms, and those ideas include: - increasing CAR activation and down-regulating the inhibitory microenvironment at the same time – genetic engineering of CAR in a way hat they become resistant to the inhibitory cytokines – targeting the cellular component of the tumor stroma – employing the clonal restriction of mature B cell tumors in that they express either κ or γ chain, so a CAR directed against cells expressing κ light chain are selective and effective with sparing of other cells expressing γ (39). Also, monoclonal antibodies against T-lymphocyte associated

antigen 4 (CTLA-4) and programmed death (PD-1) receptors may lead to signal down-regulation and help CAR cells overcome the check point inhibition. The last trend seems to be promising in lymphoma (40). Finally, much effort should be carried out to make CAR treatment approaches more popular through decreasing preparation costs and improving selectivity against malignant cells at the same time.

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