

Non-Hodgkin Lymphoma's Therapy by CAR-T Cells

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Abstract

Lymphoma is a type of cancer that causes the proliferation of B or T cells in lymph nodes. Lymphomas can be characterized in Hodgkin Lymphoma and Non-Hodgkin Lymphoma (NHL), which account for about 85% of lymphoma diagnoses. The IS has the innate ability to identify and eliminate cells with tumor potential. Despite this, our body sometimes can't combat this type of pathologies alone due to the mechanisms of tumor escape. T cells, which are very important cells in antitumor activity, have been studied and some trials show that the use of CAR-T cells may present an added value for the treatment of this type of pathologies. The CAR-T cells are genetically modified T lymphocytes to express the specific antibody binding site, directing autologous polyclonal T cells to bind to a specific Tumor Associated Antigen. The design and structure of CAR-T are determinant factors in the success of therapy. Four generations of Chimeric Antigen Receptors (CARs) are known and the difference between them is in their signaling and costimulatory domains, such as CD28 or CD137 (4-1BB). Recent studies show effectiveness in certain cases of patients diagnosed with NHL and it is recognized that the combination of complementary immunotherapy enhances the effect of CAR-T cell therapy. There is still a need to clarify which the most appropriate design and which the ideal dose to maximize efficacy and reduce the toxicity of this therapy.

Keywords: Adaptive T cell therapy; CAR-T cell therapy; Immune system; Non-Hodgkin's lymphoma

Introduction

The estimated number of new cancer cases diagnosed worldwide in 2012, was around 14.1 and about 8.2 million people died of this pathology. Cancer can be associated with individual characteristics, idiosyncratic variability, environmental exposure and lifestyle. Factors such as age, alcohol, tobacco, obesity and pollution can influence the onset of cancer [1]. The lymphoma is a group of malignant neoplasms that lead to a proliferation of B or T cells in lymph nodes. We can characterize lymphomas into two groups, Hodgkin's Lymphoma (HL) and Non-Hodgkin's Lymphoma (NHL). NHL accounts for approximately 85% of all lymphomas and arises from subpopulations of white blood cells, mostly B cells. This pathology may affect the central nervous system, bone marrow, lymph nodes and a region close to the tonsils [2,3]. The immune system (IS) and its cells, such as Natural Killer cells, T cells, and others, play a key role in tumor control and suppression through diverse processes.

After recognition of tumor cells, the IS initiates defence mechanisms that aim to protect the organism. This process contemplates three phases: elimination of neoplastic cells, the balance of the tumor (editing) and escape of the tumor. Despite the IS capacity for identification and elimination, some neoplastic cells are able to survive IS elimination mechanisms. Neoplastic cells have the ability to acquire selective clones or reach the steady-state phase, events that hamper the ability of the IS to control the proliferation of these cells. On the other hand, the IS may also harm the organism because the existence of chronic and persistent inflammation leading to cancer proliferation. This happens on account of factors such as genotoxic stress production, promotion of angiogenesis and tissue invasion, mechanisms that benefit the tumor microenvironment [4].

T cells are a very important subset of IS cells for an immune response and due to this, they are being used and studied currently as immunotherapy strategies. Adoptive T-cell therapy is an area

of the immunotherapy that relies on the transfusion of T cells [1,4]. These cells can infiltrate the tumor and, when engineered, they can also acquire the ability to express specific receptors. These receptors may have the capacity to recognise the tumor antigens (Ag) and, in the case of chimeric Ag receptors (CARs), mediate the regression of the tumor [1]. The CARs are modified receptors that target surface molecules, conferring T cells specificity for native cell surface Ag (Ag). CAR T cells are more potent than monoclonal antibodies (also used in immunotherapy) and have the advantage of being able to provide prolonged immunity against the target Ag after a single infusion [5]. The aim of this systematic review is to understand the main mechanisms used by CARs T cell in NHL treatment and their outcome.

Materials and Methods

The literature used in this review was available in databases as "PubMed" and Coimbra Health School's Library resources. The keywords selected were "Adaptive T Cell Therapy", "Non-Hodgkin's Lymphoma", "CAR-T Cell Therapy," and the "Immune System", according to Medical Subject Headings Mesh. The inclusion and exclusion criteria were defined in order to guarantee the relevance and validity of the information. Therefore, the inclusion criteria were scientific articles, clinical trials (humans) or systematic reviews (humans), with a publication date equal to or less than 5 years,

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availability of free full-text. The exclusion criteria were scientific articles not written in English [6].

Results

NHL, T cells and immunotherapy

NHL (as well as HL) occurs in rich immune lymphoid tissues and is therefore easily accessible by antibodies, the fact that makes it an excellent target for cellular immunotherapy. In addition, lymphomas express tumor Ag (e.g., CD19) and single tumor Ag that can be targeted by antibodies and/or effector cells [7].

As we can conclude from Table 1, T cells are very important cells throughout the process of immunovigilance and anti-tumor response. Thus, there is a need to target and manipulate T cells in order to increase endogenous antitumor immunity. The success of genetically engineered T cells therapy is dependent on engraftment and persistence of the modified cells. The genetic modification of T cells to confer tumor Ag recognition is typically made by transgenic expression of a high affinity T cell receptor or CAR. Conventional chemotherapeutic agents exhibit high toxicity which can be reduced through the use of engineered immune cells because of the precision and specificity with which therapeutic targets are recognized. Activation of T cells is accomplished through multiple signaling cascades induced by

Title	Authors	Publication Year	Type of study	Subject
Car-T cell therapy for lymphoma	Calcagno C, Lobatto ME, Robson PM, Millon A.	2016	Review	Non-Hodgkin and Hodgkin's lymphoma are good targets for immunotherapy. Because of their capacity of circumvent some of the major mechanisms by which tumors avoid MHC-restricted T cell recognition, CAR's are a great promise in study for lymphoma's treatment. Despite their advantages CAR's have showed some toxicity's effects.
Advances in cancer immunology and cancer immunotherapy	Voena C, Chiarle R.	2016	Review	Advances in immunology lead to new therapeutic approaches of cancer's treatment. Is important know the biology of the tumor and his interaction with the immune system in order to develop and maximize new strategies against cancer. T cell based treatments are currently under investigation for different types of tumors.
CD19-targeted CAR T cells: A new tool in the Fight against B cell malignancies	Miller BC, Maus M V.	2015	Review	CAR T cells are reprogramed to attack cells expressing the target extracellular Ag. CAR's have 4 domains which are the extracellular Ag binding domain, a hinge region, a transmembrane domain, and an intracellular signaling domain. The different generations of CAR design contain different intracellular signaling domains. Each successive generation adding additional costimulatory domains. Despite the advantages, CAR T cells present potential for significant toxicity.
Toxicity and management in CAR T-cell therapy	Bonifant CL, Jackson HJ, Brentjens RJ, Curran KJ	2016	Review	A better understanding of the response of the immune system after infusion of T-cell CAR will allow an improvement in treatment and scientific knowledge, which will allow the reduction of the inherent risks. In the future, the toxicity resulting from this therapy is expected to be anticipated and controlled, in order to improve the therapy's quality.
CAR T-Cell therapy: The role of physical barriers and immunosuppression in lymphoma Gunilla	Enblad G, Karlsson H, Loskog ASI	2015	Review	CAR's consists of an Ag recognizing extracellular domain and an intracellular signaling domain. Their design have influence in the therapy's response. Despite this exist others physical barriers of CAR T cell infiltration. Solve CAR T cell accessibility and survival in lymphoma is very important to improve these therapies.
Novel immunotherapies in lymphoid malignancies	Calcagno C, Lobatto ME, Robson PM, Millon A	2015	Review	CAR T cells therapy reach promising results. Because of this fact immunotherapies may become one of the central components of treatment strategies in lymphoid malignancies. Is important to know the microenvironment associate with these tumours and understand the difference in efficacy of this therapy in the different pathologies. Is also need to know the mechanism of action of each treatment modality to manage and sequence each treatment option for the patient.
CD19-targeted T cells for hematologic malignancies: Clinical experience to date	Davila L M, Sauter C, Brentjens R.	2015	Review	CAR is composed of antigen-binding domains fused to cell activation and costimulatory domains. CD19targeted CAR T cell are successful against B-ALL malignancies, establishing themselves as a potential for cancer's treatment. The observation of an early efficacy signal guarantee development of this modality into future immunotherapeutic cancer's therapies.
Chimeric antigen receptors for the adoptive T cell therapy of hematologic malignancies	Davila ML, Bouhassira DCG, Park JH, Curran KJ, Smith EL, Pegram HJ, et al.	2014	Review	CD19 is expressed in malignant B-cell disease being expressed as a limited form in B cells, but not in bone marrow stem cells. For this reason, CD19 was chosen as a target for B cell malignancies. The genetic modification of autologous T cells with CARs represents a breakthrough for cancer's therapy for hematologic malignancies.
CAR T-cells merge into the fast lane of cancer care	Frey N V., Porter DL.	2016	Review	CARs redirect T cells to target specific tumor Ag. CAR-modified T cells with CD19 cells showed remarkable activity against malignant neoplasms, including B-cell acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), and non-Hodgkin's lymphoma (NHL). Different generations of CARs have different outcomes, what inspire the exploration of new generations.
Chimaeric antigen receptor T-cell therapy for tumour immunotherapy	Sha H, Wang D, Yan D, Hu Y, Yang S, Liu S, et al.	2017	Review	Therapies using CAR-modified T cells against CD19 is a highly effective immune treatment for B-cell malignancies. There have been many trials of CAR T cells directed other tumour specific or associated Ag in various hematologic malignancies and solid tumours. Despite the promise of success is necessary to found a way to limit or contain CAR T cell therapy's side effects.
Recent advances in engineered T cell therapies targeting B cell malignancies	Singh N.	2016	Review	Several clinical trials have demonstrated the success of T cell therapy for B cell malignancies. Efficient engineering, appropriate target selection and synthetic receptors with potent T cell activating domains has led to the development of highly-active cellular therapy.

Table 1: Bibliographic reviews insert in this review.

Ag presenting cells. For complete T-cell activation, Ag recognition signals must be detected by TcR stimulation in combination with co-stimulation across a range of proteins such as CD28, CD27 and 4-1BB. Despite this, serious adverse effects were observed after infusion of CAR-T cells in host individuals. These adverse effects (consequent to CAR-T cell therapy) can be immediate, delayed, mild, severe and/or persistent over the lifetime of the genetically modified T cells. Toxicity caused by this therapy includes cytokine release syndrome (CRS), neurological toxicity, on-target/off-tumor recognition, insertional oncogenesis, and anaphylaxis, graft *versus* host disease and off-target Ag recognition. This toxicity can be managed through pharmacological immunosuppression, suicide genes, elimination genes and targeted activation [8-11].

Car T cells

CAR T cells are autologous T lymphocytes that are genetically modified to express the specific antibody (Ab) binding site, directing autologous polyclonal T cells to bind to a specific tumor associated antigen (TAA). CAR-T cells can be used to target a highly and consistently expressed lineage-specific Ag (e.g., CD19, CD20, CD22). This results in elimination of malignant B cells [7,12]. CARs are hybrid molecules composed of antigen-binding domains fused to the T-cell activating and costimulatory domains. The antigen-binding domain of an Ab re-created as a single-stranded variable fragment (scFv) and is expressed on the cell's surface. The synthetic nature of CARs allows these to be capable of targeting a variety of cancers by replacing multiple antigen-binding domains [13,14]. The CARs present 4 domains, which are an extracellular Ag binding (ectodomain), a hinge region, a transmembrane domain and an intracellular signaling domain (endodomain). The antigen-binding domain recognizes the extracellular Ag in their native form and does not require presentation in an MHC molecule. This will allow the CAR to function independently of the haplotype of the patient and still allow it to be used against many different extracellular ligands [7,9]. Many aspects of CAR design, such as epitope selection, affinity, hinge region length, and comparison of different combinations of intracellular signaling domains, is still under active investigation. The first generation of CAR contained a single intracellular signaling domain (CD3 ζ) that transmitted signals to the T cell. This generation has a limited activity and this is probably due to the inability of first generation CARs to properly activate T cells, especially in cases where tumor cells did not express T cell costimulatory molecules. The activation and proliferation of T cells were at a low level which eventually resulted in low antitumor efficacy. Subsequently, the second generation of CARs containing one or more costimulatory domains (CD28 or CD137 (4-1BB)) was designed, leading to improvements in T cell proliferation and persistence. Preclinical studies suggest that 4-1BB CARs can produce improved expansion and persistence *in vivo* and 4-1BB. Third generation CARs incorporate two costimulatory domains, the former being either a CD28 or a 4-1BB domain and the latter provided by other molecules, such as OX40, CD28 or 4-1BB36-39. Fourth generation CARs, also known as "TRUCK" T cells, are designed to also express co-stimulatory cytokines or ligands, which aim to increase the expansion and longevity of T40 CAR cells [9,12,15,16]. Second-generation CAR-T cells are more efficient than first-generation CAR-T cells. Apparently, to ensure the success of CAR-T cell therapy, pretreatment lymphoplasty clearance prior to the infusion of CAR-T cells is required. Tumor-reducing chemotherapy and chemotherapy with lymphomaplasmia are excellent allies for CAR-T cell therapy, and when administered prior to the infusion of CAR-T cells can improve the safety and efficacy profile of this treatment by reducing a number of cells inflammatory reactions in the tumor microenvironment and

forming a niche for the expansion and persistence of CAR-T cells [11]. Experimental studies point to a synergistic effect between CD28 and 4-1BB, whereas T cells stimulated by CD28 and 4-1BB have higher antitumor activity and greater persistence *in vivo* compared to T cells stimulated by any of these separately [10].

Advantages and disadvantages of CARs Use

CAR-T cells have the ability to bypass some of the major mechanisms by which tumors prevent recognition of MHC-restricted T cells, such as down regulation of human leukocyte antigen (HLA) class I molecules and defective Ag processing. CAR-t cells are also able to target non-protein Ag, allowing them to recognize lymphoblastic tumor Ag derived from carbohydrates or glycolipids. This ability is shown to be an advantage since the conventional T cells receptors (TCRs) can't detect these Ag. In spite of this, the TCRs can bind any Ag that is presented by the MHC (major histocompatibility complex), including intracellular proteins, while CARs are only able to bind cell-surface molecules [7,17].

Cars's expression

CAR-T cells must be transplanted into a subset of T cells that have the ability to target tumors. *In vivo* studies on the application of $\alpha\beta$ -TCR+ in lymphoma, therapy aim to identify, through the phenotypic profile, the ideal subset within this population. T cells that exhibit a memory-associated phenotype promise to be important for the *in vivo* persistence thereof. Some studies performed in which cells expressing a memory-associated marker (CD62L) to express CARs directed by CD19 were selected. Recently a subset of T cells that have a greater proliferative potential and greater survival *in vivo* has been identified. As an alternative to T cell selection based on the surface phenotype there is still the physiological selection of T cells, which have the ability to act as effector T cells, enter the memory group and re-expand on Ag re-exposure *in vivo*. There is another type of T cell, virus-specific T cells (VSTs) which in addition to this aforementioned characteristic further express chemokine receptors that allow movement to lymphoma sites. The ability of these cells to interact through their native TCR with viral Ag on Ag presenting cells enables the occurrence of various signals with stimulators that increase their persistence after adoptive transfer, increasing their antitumor activity [7]. The fact that most CARs based on a single-chain variable fragment (ScFv) only recognize intact target Ag and expressed directly on surface cells, and also recognize peptide fragments of processed proteins that limit and hinder the ability of CAR-T cells to detect. The majority of tumor-specific antigenic epitopes [7]. CAR-t cells can be used to target a specific and consistently expressed Ag (such as CD19, CD20 and CD22), which leads to the elimination of malignant B cells which have the common side effect of B cell ablation. This side effect is relatively benign since intravenous Ig replacement therapy is feasible and circumvents the situation. However, it may be preferable to target Ag associated with restricted strains, such as the B cell maturation Ag (BCMA) [7]. In T-cell lymphomas, segmentation of an entire lineage is not as feasible or acceptable, because unlike B-cells, the T-cell function is less accessible to replacement therapies. However, a more selective marker for a T cell line, such as CD30, may be an acceptable option, particularly if its expression on tumor cells is high [7]. Segmentation of single Ag implies an inherent risk of immune leakage, which can be reduced by multiple Ag. Thus, expressing various CARs on T cells will potentially increase safety by generating T cells that recognize a unique Ag pattern that is only expressed in tumor cells or in their associated stroma [7].

CAR's effectiveness

Many tumors, including most lymphomas, have the ability to secrete immunosuppressive cytokines, attract immunosuppressive cells, and express molecules on the cell surface that suppress immune cells, inhibit maturation of dendritic cells, and still have the ability to create an immunosuppressive metabolic environment. Although CD28 or 4-1BB endodontically mediated T cell costimulation in CAR molecules may mitigate some of the inhibitory effects resulting from tumor cells, other causes of energy are more difficult to combat. To overcome tumor immunosuppression, countermeasures were adopted that aim to circumvent the effects of tumor cells on the IS. These approaches include increasing the level of CAR-T cell activation or decreasing physiological down-regulation by point-of-control molecules, altering CAR-T cells by engineering so that they become resistant to inhibitory cytokines released by the tumor, and still the targeting of the cellular components of the tumor stroma [7]. An important fact to consider is that regulatory T cells and myeloid-derived suppressor cells are immunosuppressive cells that impair the function of CAR-T cells. Thus, there is a need to reduce its concentration by administering chemotherapy with aggressive agents so that CAR-T cells can perform their function and ensure the effectiveness of this therapy in different types of lymphomas [11]. T cells are serial killers that have the ability to expand and survive, under appropriate conditions, killing tumor cells. These can survive *in vivo* as effector memory cells. While an Ab only has the potential to bind only to a tumor cell and thereby induce antibody-mediated cytotoxicity, T-CAR cells proliferate *in vivo* and have the ability to go from tumor to tumor performing the sustained cytotoxic activity [11].

CAR T cell's barriers in lymphomas

A lymphoma is a type of solid tumor, which can cause the CAR-T cells to have some difficulty in making contact with tumor cells. A solid tumor may have a higher level of immunosuppression, with regulatory immune cells and inhibitory as proteins being concentrated in the vicinity of the tumor. CAR-T cells may also be devoid of localization receptors that allow them to penetrate solid tumors, which hinder the

entire process of tumor attack. The fact that effector T cells are subject to circulation leads to them not returning to lymphatic tissues, which may disrupt the clearance of tumor cells present in the lymph nodes [11].

Discussion and Conclusions

CAR-T cells are a promising therapy to combat cancer, specifically NHL. These cells reveal the ability to bypass the mechanisms of tumor escape. Physical barriers prove to be a crucial factor in the success of this therapy. Studies have shown that these barriers can be overcome through the use of appropriately designed CAR-T cells. The differences between the different generations of CAR-T cells are in their signaling and costimulatory domains, which impart more or less efficiency to them [11]. The first clinical trial to demonstrate the significant efficacy of engineered t-cell therapy in the treatment of lymphomas contemplated nine patients with diffuse large B-cell lymphoma (DLBCL) and six patients with various indolent lymphomas. Of the 13 patients that were evaluable, 12 (92%) achieved an objective clinical response and 8 (62%) achieved complete responses lasting > 23 months [17]. As we can see in Table 2, a clinical trial conducted in 2015 and developed in patients with B-cell malignancies reveals promising results for the association of chemotherapy regimen of cyclophosphamide and fludarabine with anti-CD19 CAR T cells (single infusion). Although one of these patients died without a known cause, the results of this trial are very promising, resulting in three positive clinical conditions: complete remission, partial remission or stabilization of clinical status [18]. Another clinical trial was conducted in 2013 in patients diagnosed with different types of lymphoma. As described in Table 2, these patients received a treatment of anti-CD19 CAR T cells and also showed promising results that translate into clinical profiles similar to those previously reported, although two patients did not respond positively to therapy [19]. It is now known that there is a synergistic effect on the association of other immunological therapies (such as chemotherapy, radiotherapy) with CAR-T cell therapy. This is a very interesting association given that the antitumor activity is amplified and the results obtained are quite promising [11]. To optimize this type of therapy it is then necessary to

Title	Author	Publication year	Type of study	Samples	Methods	Results
Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 Chimeric antigen receptor	James N. Kochenderfer, Mark E. Dudley, Sadik H. Kassim, Robert P.T. Somerville, Robert O. Carpenter, et al.	2015	Clinical Trial	Fifteen patients with advanced B-cell malignancies were treated. (Nine patients had diffuse large B-cell lymphoma (DLBCL), two had indolent lymphomas, and four had chronic lymphocytic leukemia)	Patients received a conditioning chemotherapy regimen of cyclophosphamide and fludarabine followed by a single infusion of anti-CD19 CAR T cells	Eight patients achieved complete remissions (CRs) Four patients achieved partial remissions One patient had stable lymphoma Two patients were not evaluable for response One patient died 16 days after cell infusion (of an unknown cause) Toxic effects like fever, hypotension, delirium, and other neurologic toxicities occurred in some patients after infusion of anti-CD19 CAR T cells (these toxicities resolved within 3 weeks after cell infusion)
Donor-derived CD19-targeted T cells cause regression of malignancy persisting after allogeneic hematopoietic stem cell transplantation	James N. Kochenderfer, Mark E. Dudley, Robert O. Carpenter, Sadik H. Kassim, Jeremy J. Rose, William G. Telford, et al.	2013	Clinical trial	Ten patients with different types of lymphoma were treated. (Four patients had mantle cell lymphoma (MCL), four had Chronic lymphocytic Leukemia (CLL) and two had diffuse large B-cell lymphoma (DLBCL))	Patients received a treatment of anti-CD19 CAR T cells	Six patients stable disease were staged as "stable disease" after anti-CD19-CAR T-cell infusion One patient obtained an ongoing complete remission after anti-CD19-CAR T-cell infusion -One patient obtained an ongoing partial remission after anti-CD19-CAR T-cell infusion -Two patients had progressive malignancy after anti-CD19-CAR T-cell infusion

Table 2: Clinical trials insert in this review.

understand and know the immune response after infusion of CAR-T cells. This knowledge provides information and makes it possible to expand studies on the activation or elimination of CAR-T cells, which reduces risks after infusion [10]. It is also interesting to identify the ideal dose of CAR-T cells to guarantee the success and maximum use of the therapy, a dose that is yet to be defined. This is a difficult task due to the resulting variation in cell expansion *in vivo*. This fact also imposes some questions of patient safety because it predisposes the inconsistency of the response and the toxicity they may or may not exert on the organism [12]. Although the CAR-T cells present some difficulty in penetrating solid tumors, such as the NHL. Therapy with these cells proves to be promising for patients with this diagnosis, although it is still necessary to advance in the design studies of CAR-T cells, the dose to be administered and the ideal combination of immunotherapies to be used. In this way, the beneficial effects of this therapy can be maximized and the side effects and toxicity inherent in it diminished.

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