EVOLVING ROLE OF CAR T-CELL IN CANCER IMMUNOTHERAPY

AMAL A. SULAIMAN[1*], ZAINAB AMER Al-SHAMAA[2], MOHAMMAD EMAD Al-ASSADI[2]

[1]Department of Therapeutics and Clinical Pharmacy/Faculty of Pharmacy/Baghdad College for Medical Sciences/Baghdad, Iraq,
[2]Graduated pharmacy students
Email: amal3_@yahoo.com

ABSTRACT

Safety profiles of newly developed anti-cancer therapies is the main goal for efficient treatments to improve survival rates. Therefore, continuous efforts carried out to develop a therapeutic strategy with better outcomes. The concept of immune-oncology, which utilizes and enhances the capacity of human immune system was developed as an eventual opportunity to enhance remissions and limit the relaps of the disease. Later progression of cellular immunetherapies involve the introduction of genetically engineered T cells having chimeric antigen receptors (CARs) that embraced an antibody-derived antigen recognition domain connected to an internal T-cell signaling domain, so can recognize their targets with high degree of tumor selectivity. This approach showed vigorous antitumor outcomes and full recovery in end-stage patients suffering from liquid cancers as leukemia and lymphoma. However, still there is a challenge for bringing genetically modified T-cell immunotherapy to many patients with different tumor types including solid tumor. On other hand, studies indicated the potential to broaden T-cell–based therapies and foster for other possible applications beyond oncology as organ transplantation and autoimmunity. Therefore, this review aimed to illustrate the clinical applications, challenges, and approaches for more efficient clinical employment of CAR T cell therapies.

Keywords: Cancer, Immunotherapy, CAR T cells

INTRODUCTION

Over the past decades, increased evidence howed that the use of traditional cytotoxic strategies in the management of neoplastic disease showed a marked drawback because of their low selectivity and development of drug-resistance cancer cells [1-3]. Moreover, the lack of an efficient approach to completely eleminate malignant cells rise the need for more effective therapies. Recently, the concept of cancer immune therapy has been emerged as a new challenging pathway that alters the features of cancer treatment. Where, they get use of normal ability of the immune system in treatment of sever illness as cancer [4, 5]. However, the cellular immunotherapies that bind and augment the natural capacity of the immune system to fight cancer has been investigated for treatment of human immunodeficiency and tumor [6, 7]. The principle of covey the immune response to combat tumor based on understanding the interplay between cancer and immune sysrem that often involve the following interactions; i) Initial recognition of "nonself" antigens from invading pathogens or infected/malignant cells; ii) selective attacks and destroys of causative agents whith out affecting the normal host cells; and finally iii) establishing an immunological memory mediated by adaptive immune system to provide a protection against further attack of the host [8-10]. This sequence of organized step-wise events commonly named (cancer immunity cycle), through which the immune system acquired properties that induce an immune reaction called immunoediting, which provides a balance between immune surveillance and cancer progression [11, 12]. Immunoedting comprised three primary phases: elimination, equilibrium, and escape that often contribute to cancer elimination, dormancy, and progression, respectively [13, 14]. Interestingly, this capacity of cancers to evade the immune response is now recognized as one of the most characterstic cancer hallmarks, that provides the platform for treatments within the milieu of immunotherapies [15, 16]. In this regard, this study concerned with later findings in cell immunotherapies that developed as a potential therapeutic intervention for cancer treatments.

Cancer immunotherapy

An accumulated evidence indicated that both immune systems and cancer cells are often present in a state of dynamic balance producing an immune response which either eradicates tumor cells or offers a chance for tumor to escape immunologic elimination [17]. Accordingly, various therapeutic strategies have been developed, by which the immune system possess anticancer effect as immunostimulants, Monoclonal antibodies, Autograph or allograph transfer of lymphocytes, cancer vaccines and immunomodulators. However, the common impact of cancer immunotherapies is to reactivate the immune system to easily recognize tumor cells again, and inducing an immune-mediated control of cancer, either through either a passive or active processes conferring direct lysis of cancer cells [18, 19]. For passive type, the machineries of the host immune system were utilized to target and combat tumor antigens as with the use of, tumor-targeting monoclonal antibodies (mAbs), cytokines like Interleukins (IL-2, IL-12), Interferon's (IFNs) and in some approaches they use adoptively transferred T cells. These treatments usually possess an intrinsic antineoplastic activity. On the other hand, the active immunotherapy aimed to boost the host's immune system to defend against cancer, as with the use of checkpoint inhibitors or different types of anticancer vaccines, including (cell-based, peptide or protein-based, gene therapy-based, idiotype immunoglobulin based and autologous or allogeneic Whole-Tumour-Cell)vaccines. Where their anticancer properties employed only upon engagement with the host immune system. [20]. While, later classification based on treatment specificity against tumor antigen, where, the nonspecific immunotherapy make use of cells or substances that are not directed to a specific antigen as with immunostimulatory cytokines or checkpoint blockers which are activated broad specifity of anticancer immune responses [21]. Conversely, instructing the immune system to generate a T cell response against tumor-specific antigen (TSA), or tumor-associated antigens (TAAs) that are presented by specilazied APC denoted as active specific immunotherapy [22, 23].

Adoptive cell therapy (ACT)

A strategy of immunotherapy was directed for the treatment of progrssed tumor. This can be done by manipulation of patient's own T-cells ex vivo, so can fight the diseases; effectiveness of this strateegy usually based on the availability of sufficient number of active antitumor T cells named as adopted T cells (ACT) to efficiently regress cancer [24]. In this strategy a particular variant of cell-based

anticancer immunotherapy was utilized to involve; the identification and collection of circulating T lymphocytes of patient have anti-tumor activity called tumor-infiltrating lymphocytes (TILs); after selection, cells exposed to modification/expansion and grown ex vivo up to 1011, and subsequently further activation step carried to give high avidity recognition by tumor antigen-presenting cells together with release of *in vivo* inhibitory factors. Finally, the activated cells infused back to the same patient to provide a favorable microenvironment that better supports antitumor immunity [23, 25]. To perform these steps, the patients may experience a condition known as lymphodepletion by the use of chemotherapy or irradiation to counteract the immunosuppressant effect of regulatory T cells (Treg), as well as to minimize the competitive effects of other lymphocytes with the transferred cells for various factors involved in T-cell survival like growth factors or interleukins 2, 7 and 15 (IL2. IL7 and IL15) [26].

Clinically, they use of (young TIL) as an alternative strategy for ACT, where young lymphocytes isolated from patients allowed to grow up for short term ex vivo, then reintroduced again into the patient. This approach of immunotherapy provides about 56% regression of variety of cancer including those of bone, liver, brain and lymph nodes [27]. Although, the use of lymphocytes expanded from a tumor biopsy sample, and endogenous antigen-specific T cell from peripheral blood are hopeful and efficient immunotherapeutic regime, but the inaccessible tumor sites, poor TIL recovery, poor antigenicity of some tumors, and the demanding of intensive laboratory applications make the treatment hard to produce and roadblocks the expanding of TIL therapy as a global cancer therapy option. However, the main issue with ACT is the fact that it is a highly personalized treatment where a new and different reagent has to be created each time for each patient. It relies on activated cells with lowered triggering thresholds for clinical benefit but does not enrich for TAA specific T-cells [28]. Therefore, third strategy has been developed to improve the therapeutic potential of ACT. For instance, genetic engineering has been employed to endow peripheral blood lymphocytes (PBLs) with features such as unique antigen specificity, increased proliferative potential and persistence *in vivo* for developing TAA specific T-cells is to engineer them with artificial TAA-specific receptors e. g. a new TCR or a chimeric antigen receptor (CAR) [26, 29].

Genetically modified t cells in cancer therapy

T cells or (T lymphocytes) widely distributed within tissues and tumor environments. They play an essential role in cell-mediated immunity and involve in long-lasting antigen-specific effector and immune memory responses. Usually, T cells expressed T cell receptors (TCRs) on their surface providing a single antigen-binding site. The TCR consists of two chains: the alpha (α) and beta (β) chains. Both chains have a constant region (c) and a variable region (v), and it is the variable region that confers antigenic specificity on the T cell, moreover, TCR associated with the CD3 complex, which consists of three transmembrane signalling molecules (CD3ζζ,CD3δε and CD3γε). Accordingly, TCR specificity aid in recognition of an antigen ligand comprising a short contiguous amino acid sequence of a protein presented on the target cell by a major histocompatibility complex (MHC-1 for cytotoxic T cells). Efficient T-cell activation also requires the simultaneous binding of the T cell co-receptor (CD8 for cytotoxic T cells). ss, disulphide bridge [30,31]. Previous studies indicated that the use of infiltrating T cells (TIL) after being isolated from tumor tissue, cultivated, activated and expanded ex vivo, then re-infused provided a promising efficacy to induce long-lasting regression in patients with metastatic melanoma [32-38]. As well as improved prognosis in other cancer types, including ovarian, colon, and breast cancer tumor in clinic [30, 39-41]. However, there some difficulties limited the use of this strategy as the a difficulty in isolating tumor-specific T cells from many cancer patients; and the long-time consumed to gain a therapeutic amount of tumor-specific T cells. In addition tolerance has been reported [42], since the specificity of TCR was intrinsically controlled due to its dependence on antigens expressed by tumors via their MHC complexes [43]. To overcome limitations associated with tolerance, the research was directed toward utilization of genetically modified T cells which redirected to successfully target

specific antigens expressed by tumors. In particular, T cells were engineered to express modified TCRs (so-called TCR therapies) or protein-fusion derived chimeric antigen receptors (CARs) that have enhanced antigen specificity, producing more efficient T cells for targeting tumors without the requirement for de novo T-cell activation in the patient. [31]. So that the introduction of this approach allows sufficient production of antigen-specific T cells. Moreover, in clinical situation the use of engineered T cells in cancer treatment showed remarkable successes in patients with colorectal carcinoma, synovial sarcoma, metastatic melanoma, and multiple myeloma. Hence, for successful generation of tumor-specific TCR, initially a suitable target sequence must be identified, which either isolated from tumor-reactive T cell or, if not possible, using alternative technologies to get a highly active anti-tumor T-cell antigens, by one of the following [44-50].

1) Immunization of experimental transgenic animals with human tumor protein to produce T cells expressing TCRs against human antigens.

2) Isolation of tumor-specific T cells from a patient showing tumor remission and the reactive TCR sequences then conveyed to T cells obtained from another patient who has a disease but not-responsive. This called Allogenic T cell transfer approach.

3) Intensify the killing reactivity of T cells against tumor and rising the potential interaction of a feebly reactive tumor-specific TCR with target antigen by *in vitro* alteration of the TCR sequence [51].

Chimeric antigen receptors (CARs)

The Chimeric antigen receptor (CAR) T-cell therapy was developed to use gene transfer technology for reprogramming patient's T cells to express CARs that directed the cytotoxic potential of T cells against tumor that would otherwise be ignored [3]. The CARs are an engineered fusion proteins that contain an extracellular antigen-binding domain composed of a single-chain variable fragment derived from an antibody and intracellular signaling domains, which are involved in the initiation of T-cell signaling and downstream T-cell effector functions [4, 52]. The interest and investment in the development of CAR T-cell therapy is rapidly increasing in both academia and industry, with multiple ongoing clinical trials as well as many expectations for the future of the field. Although CAR T-cell therapies are on a fast track to approval by the US Food and Drug Administration for B-cell malignancies, there is active investigation into building better CAR T cells for treating hematologic malignancies and solid tumors. The technique of Gene-transfer was known in 1990s and called "T body approach". Nowadays these artificial lymphocyte signaling receptors were restructured the specificity of T cells that commonly referred to as chimeric immune receptors (CIRs) or chimeric antigen receptors (CARs). Where, TCR part is replaced by CAR which includes two domains: an extracellular derived from tumor-specific antibody single-chain fragment (scFv) having specificity against a cell surface antigen and an intracellular signaling domain [53, 54] (fig. 1).

Genes encoding these receptors are inserted into patient's T cells using viral vectors to generate tumor-reactive T cells. While, the intracellular domain includes fused signaling domains from a natural TCR complex and costimulatory molecules. In general, CAR cells are essentially engineered cytotoxic T lymphocytes to target specific tumor cells, and they combined both antibody-like recognition with T-cell activating function [55]. These novel receptors initiate a functional downstream effector T-cell signaling pathway when they encounter target antigen, usually the TAA on a cancer cell. This gives the opportunity to engineer a large variety of TAA-specific receptors targeting a broad range of cancer types [56]. Once infused, CAR T cells engraft and undergo extensive proliferation in the patient. Each CAR T cell can kill many tumor cells, and may promote immune surveillance to prevent tumor recurrence through antigen release, by assisting tumor-infiltrating lymphocytes to attack tumors, or by their own persistence [57]. In other wards, CAR T cells hold antitumor activity through immune-mediated communication with target cells through the secretion of proinflammatory cytokines as interferon [IFN]-γ, and [IL-2] augmenting an endogenous immune response and partly by expression of pro-apoptotic ligands and release of perforin. In addition, CAR T cells involve in "serial killing" (i,e; ordered destruction of target cell) [58].
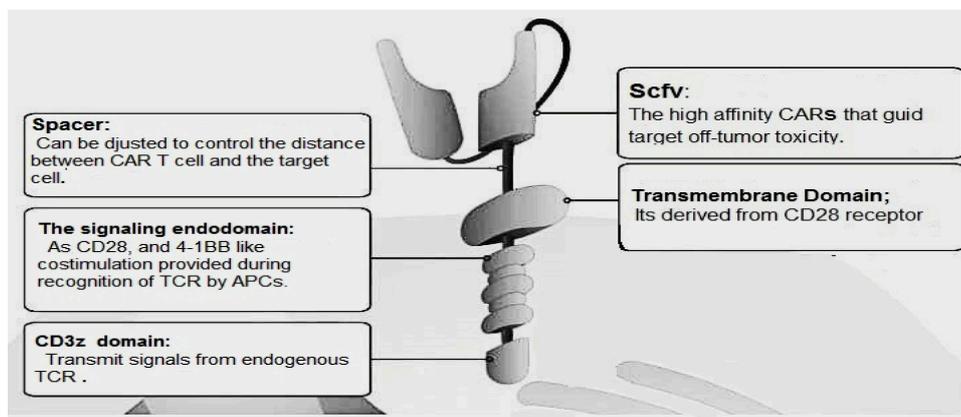
Fig. 1: Shows the CAR, which includes a single-chain variable fragment (Scfv) that binds to tumor antigens, fused to a spacer and transmembrane domain. The intracellular domain contains costimulatory domains, such as CD28 and 4-1BB and CD3z chain, which drive signal activation and amplification of CAR T cell

Generational construction

As a promising therapeutic regimen, CAR-T cell therapy has stood the test of time for many years to improve the effectiveness and safety of this approach. CAR design has developed over the past few decades as shown in (fig. 2), and now a days four different generations are available varies in the intracellular sections.

First-generation

The basic structures of CARs which known as first-generation CARs, (lack of costimulatory signal), and consist of a T-cell activating domain (typically including the chain of the CD3 complex) and extracellular immunoglobulin-derived heavy and light chains to direct specificity. This generation recognize antigen independently of human leukocyte antigen (HLA) but do not direct sustained T-cell responses, owing to their limited signaling capability. This generation of CARs transmitted activating signals only via signaling chains like (CD3ζ or FcεRIγ), licensing the engrafted T cells to eliminate tumor cells [59, 60].

Second generation

Second-generation CARs contain an additional costimulatory domain (CM I), predominantly the CD28 domain (fig. 2). Signaling through these costimulatory domain leads to enhanced proliferation, cytokine secretion, and afford anti-apoptotic functions in human primary T cells, and renders engrafted T cells resistant to immunosuppression paved the way for dual-signaling CARs that could effectively direct the expansion of functional T cells on repeated exposure to antigen [61, 62]. This generation enabled the production of the persistent "living drugs" that are the foundation of current CAR T-cell therapy. Both first and second generations showed clinical efficacy [63, 64].
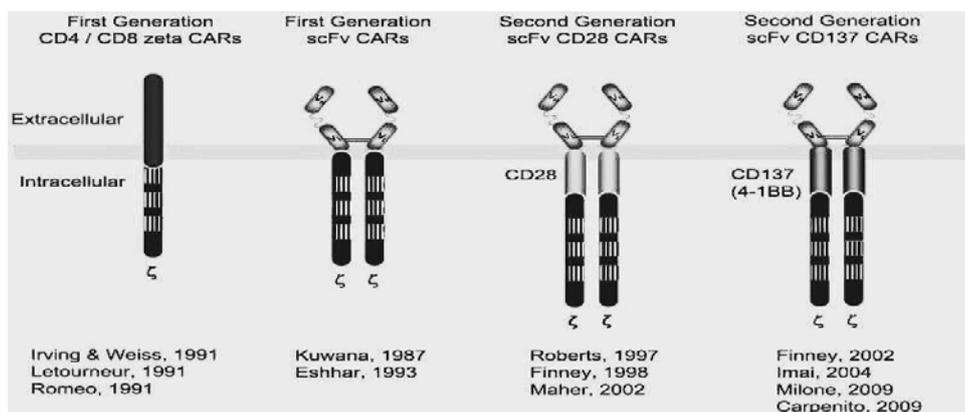

Fig. 2: A drawing of CAR T cells. Showing that 1st generation possess CD3zeta chain, or other comparable signaling domains. While 2nd generatione hav CD28 or CD137 signaling domains as they were originally described by *Kuwana* **and** *Helene Finney*

Third generation

Recent developments fused the intracellular part of a second costimulatory molecule (CM II) in addition to CD28 and Immunoreceptor tyrosine-based activation motif ITAM-bearing signaling chains of previous generations, thus generating tripartite signaling CARs. T cells engrafted with third-generation CARs seem to have superior qualities regarding effectors function and *in vivo* persistence indicating that CD28 based end domains can mediate constitutive signaling leading to terminal differentiation of effector T cells [65-67]. In general, second, third and fourth generations possess the signaling endo-domains of costimulatory molecules like CD28, CD134 (OX40) or CD137 (4-1BB), which are fused with CD3z, as shown in [fig. 3]. This structure imitates the costimulation signal when TCR combines with antigen-presenting cells to complete the process of activation.

Subsequent to the engagement of CAR T-cell antibody/ligand with target cell surface antigen, the genetically redirected T cell causing target cell cytolysis by release of cytotoxic granules containing perforin and granzymes to lyse the target cell, including drug-resistant tumor cells. A second cytolytic mechanism involves the interaction between Fas receptor (FasR/CD95) on the target cell and Fas ligand (CD95L) on the CD8þ T cell. When the Fas ligand and receptor are engaged, signaling pathways are activated in the target cell that trigger a caspase cascade resulting in target cell death [68, 69].
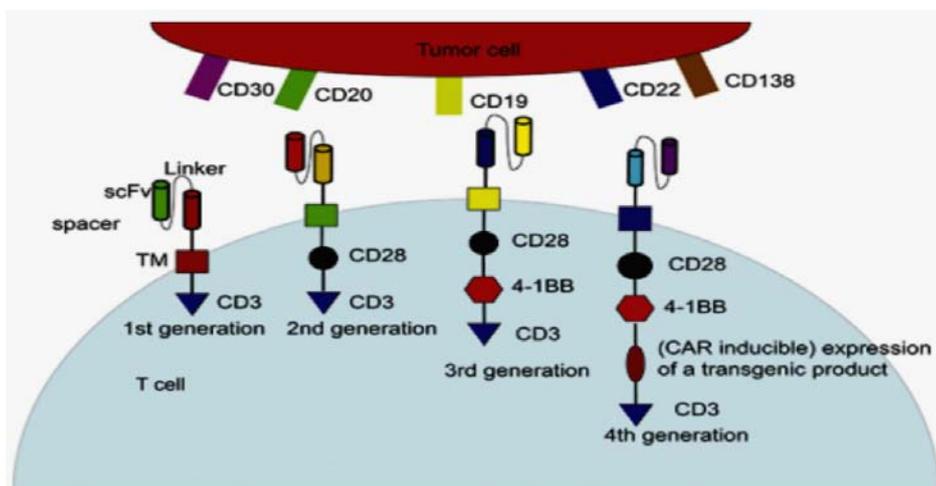
Fig. 3: Basic structure of 4 generations of (CAR-T cell) and common targets on tumor cells, showing the differences in their intracellular segments which have one or several fused signaling domain(s) from natural TCR complex and costimulatory molecules. scFv, single-chain fragment. TM, the transmembrane region

CAR T cells for B-cell malignancies

The optimal target for a CAR T-cell strategy would be a tumor type that expresses an antigen unique to that tumor and that is absent from nontumor tissue. For this reason, B-cell malignancies were the initial cancer type to become the focus of a series of clinical trials. The CD19 surface protein is a B-cell marker that is expressed on essentially all B cells, from pro-B cells to memory B cells, but not on hematopoietic stem cells. Moreover, patients appear to be able to sustain persistent reduction in numbers and function of CD19 B cells, providing that immunoglobulin replacement therapy is established. A single infusion of human peripheral-blood T cells engineered with a CD19-specific CAR was shown to eradicate established lymphomas and leukemias in mice. While, clinical trials have emerged that target a range of CD19 B-cell malignancies, including non-Hodgkin lymphoma, chronic lymphocytic leukemia, acute lumphoblastic leukemia [70-73]. Tumor regression correlates well with CAR T-cell proliferation *in vivo* and release of cytokines. Lympho-depleting preconditioning helps proliferation and persistence of CAR T-cells in some patients, which may be associated with elimination of immune suppressive cells like Tregs and increase in levels of cytokines IL-15 and IL-7 that enhanced expansion of infused T-cells and persistence of T-cells with a central memory phenotype.

The largest published series to date treating adults with relapsed or refractory B-ALL with CD19-targeted CAR T-cells are summarized in table 1.

Table 1: Clinical features of CAR T-cell of published clinical data that investigating CD19-targeted CAR T-cells in the treatment of B-ALL

Institution/ Reference	No. of patiens reported	scFv	Costimul-atory domain	Lymphodepleting chemotherapy	CAR T-cell doses	Disease-related outcomes
Memorial Sloan Kettering Cancer Center Brentjens *et al.* 2013; Davila *et al.* 2014; Park *et al.* 2018.	53	SJ25C1	CD28	Cy or Cy/Flu	1×10^6 vs. 3×10^6 CAR+ T-cells/kg	CR: 83% (MRD-negative in 67%); 17 of 44 in CR underwent allo-HSCT Median EFS: 6.1 mo (all) and 12.5 mo (pts in MRD-negative CR)
Fred Hutchinson Cancer Research Center Turtle *et al.* 2016.	30	FMC63	4-1BB	Cy 2–4 g/m2 (±etoposide 100 mg/m2 × 3 d) or Cy 30–60 mg/kg+Flu 25 mg/m2 × 3–5 d	2×10^5, 2×10^6, and 2×10^7 CAR+ T-cells/kg	CR: 10/12 (MRD-negative by flow cytometry) among pts receiving Cy or Cy/etoposide; 16/17 (MRD-negative by flow cytometry and FISH/karyotype) among pts receiving Flu/Cy Median DFS: not yet reached in Flu/Cy arm
University of Pennsylvania Frey *et al.* 2014.	12	FMC63	4-1BB	Investigator's choice	6.5–8.45×10^6 CAR+ T-cells/kg	CR: 89% (8/9) of evaluable pts, all MRD-negative; 3 non-evaluable patients died in the setting of refractory CRS
National Cancer Institute Brudno *et al.* 2016.	5	FMC63	CD28	None (administered following allo-HCT)	4.2–7.1×10^6 CAR+ T-cells/kg	CR: 80% (4/5, all MRD-negative)

Cy: cyclophosphamide, Flu: fludarabine, EFS: event-free survival, DFS: disease-free survival, CR: complete response, MRD: minimal residual disease, Allo-HCT: allogeneic hematopoietic cell transplantation.

Clinical applications of CAR T cells

CAR-T cell therapy in acute lymphoblastic leukemia

The clinical evaluation of CAR therapies has grown exponentially, with the majority evaluating the treatment of B-cell cancers. During the treatment of acute lymphoblastic leukemia (ALL), it has been found that the most effective CAR is that posses anti-CD19, which highly expressed in B-ALL to be an important target as well as anti-CD20 and immunoglobulin light chains serve as a potential target [73, 74]. CD19 is a specific protein that regulates B lymphocytes

activation and is expressed throughout all stages of B cell differentiation. It was reported that more than 1000 patients have received CD19-targeted CAR T cells, and reported data for adults and children have B-ALL. Showed promising complete remission (CR) and partial remission (PR) rates. [75, 76].

A clinical study, in which CD19 CART cells were infused following to (cyclophosphamide), revealed that 15 out of 16 patients need a qualified amount of T cells; and the CR rate was about 88% [77]. Other Studies involving children and young adult patients with age range between (1–30 y old) have found that the CR rate for the 20 B-ALL patients was 70%. [78]. recently, the CD22 has been recognized as a target for CAR T cells to overcome the limitation of anti CD19 therapy [79].

CAR-T cells therapy in chronic lymphocytic leukemia (CLL)

Currently, the only approach for the treatment of CLL is stem-cell transplantation. [80]. However, number of preliminary clinical data of CD20-and CD19-targeted CAR T-cells for B-cell non-Hodgkin lymphoma, and CD19-targeted CAR T-cells for CLL later introduced as treatment for relapsed or refractory patients and those with high risk (table 2). Some responses to the CAR-T cell in CLL patients reported equal CR and PR rates. [81-83]. Unfortunately, the pathogenesis of CLL known to induce an early suppression of immune function, therefore the efficacy of CAR-T cell therapy suggested to be hurdeled by impairment of T cells expansion ex vivo that isolated from CLL patients as well as their proliferation *in vivo*. Because of that it's essential to identify an agent to enhance the ability to prevent such phenomenon [84].

Table 2: Clinical features of CAR T-cell of published clinical data that investigating CD19-targeted CAR T-cells in the treatment of CLL

Institution	No. of patients reported	scFv	Costimulatory domain	Lymphodepleting chemotherapy	Infused cell doses	Responses observed
National Cancer Institute Kochenderfer *et al.*2012	4	FMC63	CD28	Cy 60 mg/kg × 2 d+Flu 25 mg/m2 × 5 d	0.3–2.8 × 107 CAR+T-cells/kg	ORR: 3/4 (CR, *n* = 1; PR, *n* = 2)
National Cancer Institute Kochenderfer *et al. 2015*	4	FMC63	CD28	Cy 60 mg/ kg × 1–2 d+Flu 25 mg/m2 × 5 d	1–4 × 106 CAR+ T-cells/kg	ORR: 4/4 (CR, *n* = 3; PR, *n* = 1)
National Cancer Institute Brudno *et al.*	5	FMC63	CD28	None (administered following Allo-HCT)	0.4–3.1 × 106 CAR+T-cells/kg	ORR: 2/5 (CR, *n* = 1; PR, *n* = 1; SD, *n* = 1)
Fred Hutchinson Cancer Research Center. Turtle *et al.* 2017	19	FMC63	4-1BB	Cy 30–60 mg/kg × 1+ Flu 25 mg/m2 × 3 d	2 × 105, 2 × 106, or 2 × 107 CAR+ T-cells/kg; 1:1 CD4+:CD8+	ORR: 14/19 (CR, *n* = 4; PR, *n* = 10)
University of Pennsylvania. Porter *et al.* 2015	14	FMC63	4-1BB	Investigator's choice	0.14–11 × 108 CAR+T-cells (median, 1.6 × 108 cells)	ORR: 8/14 (MRD-negative CR, *n* = 4; PR, *n* = 4) Median PFS: 7 mo Median OS: 29 mo
University of Pennsylvania. *Porter et al.* 2016.	35	FMC63	4-1BB	Investigator's choice	5 × 107 vs. 5 × 108 CAR+T-cells	ORR: 9/17 (CR, *n* = 6; PR, *n* = 3) among pts receiving 5 × 108 CAR+ T-cells

Cy: cyclophosphamide, Flu: fludarabine, OS: overall survival, PFS: progression-free survival, CR: complete response, PR: partial response, MRD: minimal residual disease, Allo-HCT allogeneic hematopoietic cell transplantation.

CAR-T cell therapy in lymphoma

CAR-T cells therapy was categorized among the most recent immunotherapies for relapsed conditions or chemotherapy-refractory B-cell non-Hodgkin lymphoma (NHL). [85, 86]. Preclinical *in vitro* and *in vivo* studies indicated effective antitumor activities of both second and third generation T cells, possessing CD28 or 4-1BB cytoplasmic signaling domains [87].

CAR T cells adverse effects and toxicity

The adverse effects are known to be associated with all cancer therapies, and CAR T cells are not an exception. Many of unwanted effects are reported with CAR T cells depend on the specificity of antibody single-chain variable fragments and T-cell activation. These effects are thus reversible when the target cell is eliminated or the engraftment of the CAR T cells is terminated. In some patients, they found that CAR T cells induce a clinical syndrome of fevers, hypotension, hypoxia, and neurologic changes associated with marked elevations of serum cytokine levels [88-90]. This spectrum of clinical and laboratory findings has been termed the cytokine release syndrome (CRS). For the investigation of cytokines, several studies surprisingly identified IL-6 as a major cytokine induced by CAR therapy. Meanwhile, IL-6 also stems from apoptotic B cells o the occurrence of this syndrome is associated with both CD19 and B-cell maturation antigen (BCMA, also known as CD269).

Intense condition of CRS may be managed initially by using the IL-6 receptor inhibitor *tocilizumab*, and when symptoms persist the addition of lymphotoxic corticosteroids is advised [84].

Other effects were observed after CAR T-cell infusion in both children and adults including the number of reversible neurologic symptoms as delirium, seizure-like activity, confusion, word-finding difficulty, aphasia, and frank obtundation. However, such symptoms found to be unrelated to CRS (63, 70, 82, 86).

Advantages of CAR-T cell therapy

The use of CARs to redirect T cells specifically against TAA-expressing tumor cells provide an advantages over former classical adaptive immune T-cells. As they have a unique specificity and can eradicate cancer cells containing the corresponding TAAs. So this approach will by-pass unnecessary killing of healthy tissues. Moreover, in contrast to the long-lasting procedure of *in vitro* selection, characterization, and expansion of T-cell clones with native specificity for MHC tumor peptide complexes, genetic modification of polyclonal T-cell populations allows generating TAA-specific T cells in one to two weeks.

In addition, engraftment with CARs having flexible intracellular signaling domains enables T cells to MHC-independent antigen recognition; thus, major immune escape mechanisms of tumors such as downregulation of MHC molecules are efficiently by-passed. Furthermore, proliferation and survival of modified T cells can be improved by the achievement of a multitude of signaling domains from different immune receptors in a single CAR [91]. Besides that, CAR-T cells not require the aid of HLA expression for recognition of cell surface molecules, so they can avoid T cell immune surveillance mediated by hiding HLA or other molecules involved in antigen processing and presentation [92]. It is valuable to point out that CAR-T cell can also identify the potential antigens in nearly all forms including carbohydrate, lipid, protein antigens, which can be combined specifically by antibodies [93].

CONCLUSION

The threshold of the golden era for adoptive T cell therapy, as advances in basic immunology have informed the development of a

new field of synthetic immunology, which may increase the potency of approaches that target cancer.

Cancer immunotherapy using genetically engeneered T cells serves as a very promising future approach for incurable cancers therapy. CAR-T cell therapy, still considers as a newley evolving approach for treatment of refractory hematological malignancies especially ALL, CLL and lymphoma and some associated adverse effects become bottleneck to the widespread use of this approach. Although that all currently available clinical studies suggested the significance of costimulation and lymphodepletion and lymphodepletion in promoting effectiveness of CAR T-cells. But still there is an urgent need for mature data to achieve right conclusions about the optimal effectiveness and safety for this therapeutic strategy. That will give physicians and patients the information and therapeutics to eliminate these malignancies.

AUTHORS CONTRIBUTIONS

All the author have contributed equally.

CONFLICT OF INTERESTS

Declared none

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