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CAR T Cell Immunotherapy That Revolutionary Breakthrough in Human Oncology Treatment: A Review

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Abstract

The discovery of CAR T cell immunotherapy, also known as chimeric antigen receptor (CAR) T cell immunotherapy, has added a new dimension to the world of cancer treatment. This is a gene-based treatment in which T cells from the patient's body are taken and genetically engineered in the lab to grow receptors. T cells containing this receptor are then injected into the patient's body to bind to the antigen on the surface area of the cancer cell and kill the cancer cell. Structurally, the co-stimulatory domain added to CAR T cells has now reached the 5th GEN of chimeric antigen receptor T cells. Chimeric antigen T cell immunotherapy is the first FDA-approved treatment for hematological malignancies that is both safe and effective. However, due to some challenges such as a lack of safety control, an immunosuppressive tumor microenvironment, ineffective T cell trafficking, and so on, CAR-T immunotherapy treatment for solid malignancy is still in the clinical phase. In the result and discussion, we have presented a survey of CAR T cell therapy with a combination of pharmacological drugs. The things we mentioned are that CAR T cell immunotherapy is innovative, suitable, elegant, and also controls synergistic anti-cancer effects. A better understanding of combinatory CAR T cell therapies provides fundamental information for improvement of those therapies, in addition to the article highlighting future opportunities, commercial advancements, and various applications of CAR T cell therapy in different cancer cells. In the entire review article, we have highlighted the neck and crop of CAR T cell therapy, from which it is easy to understand the therapy and the need for this therapy in cancer prevention and its progress.

Keywords

Cancer Immunotherapy, Chimeric Antigen Receptor, Co-Stimulatory Domain Cell Trafficking, Hematological Malignancy

1. Introduction

In the rough, oncological treatments avowed as chemotherapy, surgery and radiation therapy are either unaccompanied or in combination. Though these schemes of treatment have exploited to adequate prosperous outcome including newer and more appropriate diagnostic tool, presage of most cancer is very ponderous. In this complexity more personalized treatment such as immunotherapy obligates for most cancers to cure or control. Currently treatment or management of cancer converted into more specific therapies with immunotherapy which corroborated better individualization care and feasibility of success for each cancer patient [1].

Biotherapy is another name of immunotherapy which is naturally able to determine foreign pathogens or carcinogenic cells in the human body. Though some immunotherapy clinches the body's immune system, some of their directly bind with cancer cells [3] [4]. In human immune way, T cells or T lymphocytes carry out an exigent role, those are work to detect or shatter potential malignant or tumor cells [5]. Adoptive immunotherapy based on T cell still now develops and deals with most hematologic cancers and other cancer cells [6]. Adoptively transferred T cell therapy (ATCT) is recognized as one kind of immunotherapy that proceeds against malignancies through the seclusion of lymphocytes by potent dynamic T cells, those are infused within a patient to cure a disease [1]. Adoptive T cell transfer (ACT) clovens into three forms for cancer therapy and these are TILs (infiltrating tumor lymphocyte), TCR and CAR cell [7]. T cell receptor (TCR) or antigen receptor of T cells detects tumor antigens which acquire intense immune response within a short time to banishing tumor cells [1]. In some clinical trials, tumor infiltrating lymphocytes (TILs) proved viable complete response against meta-static melanoma. Chimeric antigen receptor (CAR) is a pretended molecule which is a protein and it fuses an extracellular antigen to dig up domain with intracellular activating domain [1]. Here we showed a comparison between CAR and TCR (**Table 1**). This CAR T therapy belongs to cellular immunotherapy that reveals antibody based chimeric antigen receptor to target carcinogenic antigen which is very proficient therapy for different kinds of hematological malignancies and solid tumors [8] [9]. In Israel first chimeric antigen receptor was discovered by Eshhar's group within 1989 at Weizmann Institute of Science. Through viral and non-viral transfection manner T cells are harvested and genetically modified and after modification these cells are patulous in culture [10]. CAR T cell is composed of two domains that deflected with TCR (T cell receptor) part of natural T cell and this domain termed as extracellular

Table 1. Comparison between CAR and TCR [2].

CAR	Factor	TCR
Single chain	Composition	Heterodimer
Surface antigen	Target	Peptide complex
Higher	Receptor affinity	Lower
Shorter (less than 2 min)	Required time to start immune response	Longer (5 to 10 min)
Linked (2nd and 3rd generation)	Costimulation	Separated
Disorganized	Formation of immune synaps	Systematic bull's eye structure
100 or less	Required number of Ag to recognize	1
Yes	Coreceptor	Yes
Yes	Serial Killing	Yes

and intracellular domain. Extracellular domain work against cell surface antigen which is an antibody single chain fragment (scFv) and intracellular domain is fused signaling domain which limns different generation of CAR T cell [11] [12]. CAR T cell production effectuate through which procedure that is complex [13]. At first without collection of granulocyte colony which is stimulating factor natural T cells collected by isolation of blood cells or phlebotomy from cellular components of blood [14]. Extension and perception of T cell may disrupt by granulocyte colony stimulating factors that's why it excluded [15] [16]. In isolation of blood apheresis is broadly used because of it cut off from its components that also helps to collect platelet and another elements of blood from patient body through blood bank and prior re-injecting it into patient body this modified genetically [17]. By transfected with CAR retroviral or lentiviral in isolated T cells converted into CAR T cells were also occurring installation of genome DNA [14] [16]. To determine effectiveness of this adoptive immunotherapy through these newly designed T cells expansion and purification is a major step [14]. At last stage of modified T cell production it takes 2 - 4 weeks for quality control and sterility test which is necessary for safe and effective treatment [16]. If patient take a conditioning treatment such as lymphodepleting at least 2 days before administration of transduced T cells it may lead to huge number of T cells expansion [14] [16]. Composition of this T cell corresponded to an antibody which have detection and binding area upon T cell surface [18]. CAR T cell have antibody like recognition power which can activate T cell through a mechanism and for this reason it got very interest in immunotherapy [19]. The scFv part of this T cell composed of on moving light chain (VL) and heavy (VH) chain that attach with each other through a linker. CAR consist of activation domain (CD-3 zeta, transmembrane domain, co-incentive domain (CD28, CD137 (4-1BB)). Eventually CAR destroy tumor cell through T cell cytotoxic function

after bind with carcinogens while T cell propagation commenced [8]. The scFv part of CAR obtain from antibody and have higher magnitude affinity than TCRs that's why it is very advantageous for cancer therapy [20]. Another cause that responsible for this therapy effectiveness is surface protein of tumor cell easily detect by scFv process [21].

2. CAR T Cell Profile

2.1. History of CAR T Cell

One of the oldest methods of cellular immunotherapy is allogenic bone marrow transplantation. Applying this immunotherapy to some patients in 1977, they found that Graft vs. Host disease emerged as a secondary disease in the patients. Later, scientists began to think about whether new immunotherapy could be invented that would not cause any secondary disease in the patient. Next, they think about T cell immunotherapy which they later genetically modify in the lab, expand and then infuse into the patient's body [22]. From their thinking, this immunotherapy is experimented in different sites and modified after a certain time interval, and finally comes to today's position, CAR T cell immunotherapy, which is accepted by the US FDA. The history of CAR T cell immunotherapy is presented in the historical diagram (**Figure 1**).

2.2. Generation of CAR

CAR Immunotherapy is one of the most common cancer treatments today. Chimeric Antigen Therapy (CAR) T is an effective treatment for a variety of hematological malignancies, such as lymphomas, acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and solid tumors like breast cancer, liver cancer, and prostate cancer [8]. The four-generation summary of CAR T cells is provided in **Figure 2**.

2.3. CAR T Cell Structure

A typical CAR T cell is made up of many parts such as extracellular, spacer, transmembrane and intracellular domain etc.

2.3.1. Extracellular Domain

The extracellular domain component is composed of a single chain variable fragment designed with a light & heavy chain variable region with a coding section of monoclonal antibody that is capable of maintaining antibody affinity [24]. These variable regions are connected to each other with glycine serine residues which are able to minimize the risk of linker interference between the domains [25]. Antigen recognition domains in CAR are able to treat against autoimmune or infectious diseases [26].

2.3.2. Spacer Domain

Spacer domains are usually bridges between extracellular domains and transmembrane domains. According to some reports, the activation of the carrier cell

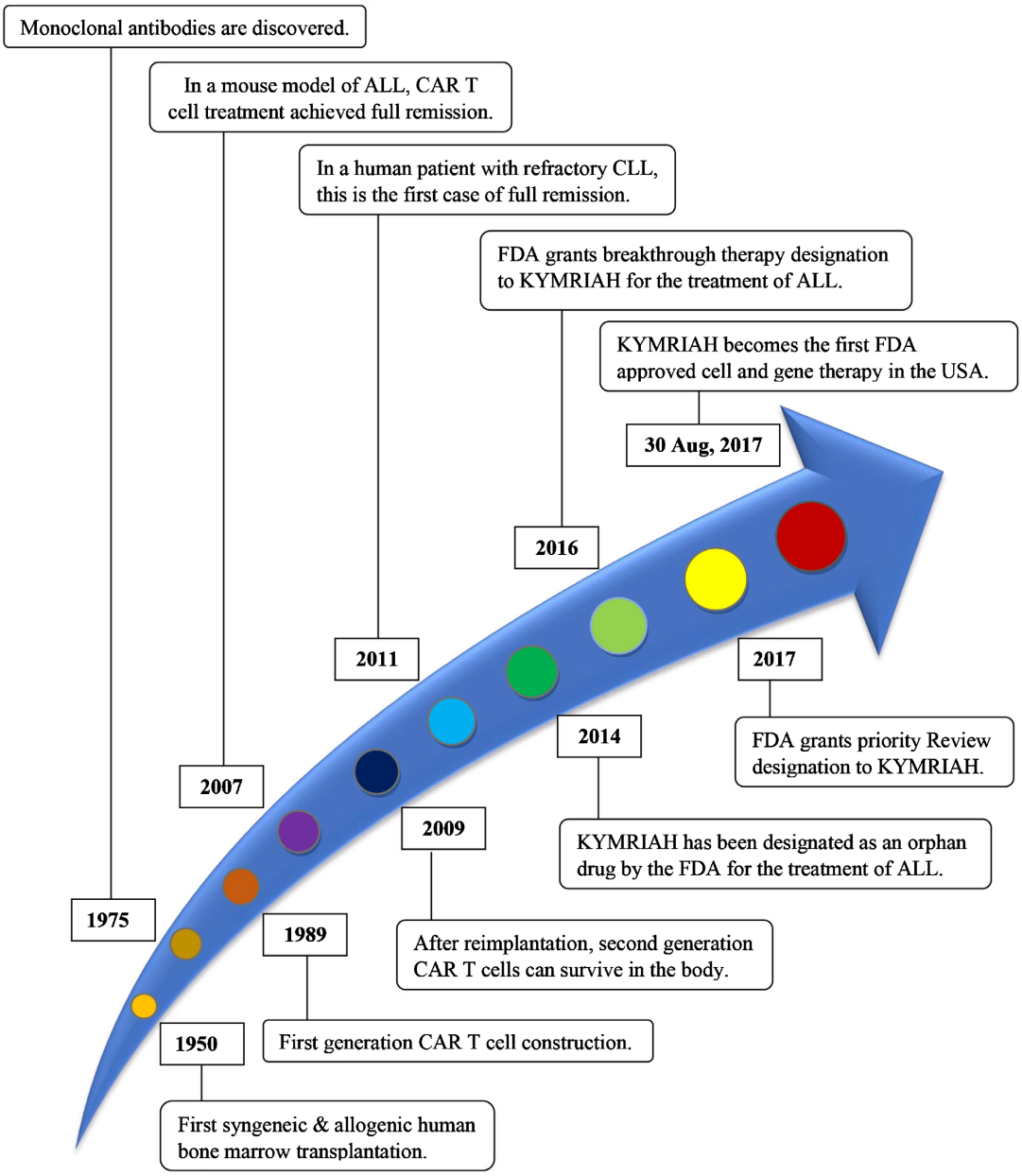

Figure 1. History of CAR T cell immunotherapy [22].

depends on the length of the spacer domain [27]. The smaller the length of the spacer domain, the greater the activation of the T cell. In many cases, the inability to bind the cell membrane to the target antigen plays an important role in binding to the cell membrane through the longer space domain Sc-Fv, although in many cases it becomes a risk because it depletes the carrier cell [27] [28]. In closing, I would say that based on the accessibility of the target antigen, I need to create an optimal length speacer domain that is able to ensure proper function of my CAR.

2.3.3. Transmembrane Domain

This transmembrane domain acts as a connector between the extracellular and

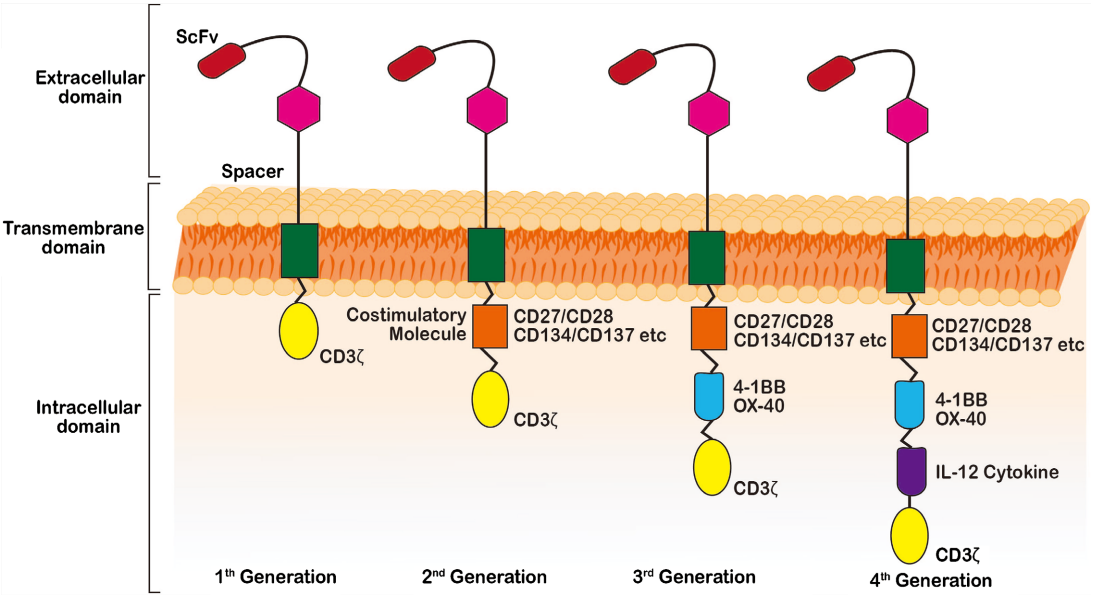

Figure 2. Four generation of CAR T cell [23].

the intracellular domains. It is made up of a hydrophobic alpha helix which is able to span the membrane. This transmembrane region of CAR T cells plays a vital role in proper synapse formation or CAR surface expression [29] [30].

2.3.4. Intracellular Domain

The intracellular domain basically activates the CAR T cell during signal passing [31]. In this study, we look at the development of a 4th generation CAR T cell which is able to overcome the restrictions of the 1st generation by adding mother domain CD3 zeta. Later, another co stimulatory domain, 4-1BB, was added to the 3rd generation to further improve the function of the CAR T cell. Finally, IL-2 cytokines were added to boost the activation of 4th generation CAR T cells.

2.4. CAR T Cell Manufacturing

In the case of CAR T cell manufacturing, first WBC has to be separated from the patient's blood, which is called the leukapheresis process [32]. The leukapheresis product is enhanced for T cells once a sufficient number of leukocytes have been extracted. Subsequently, the cells are separated by centrifugal elutriation based on their size, and it's activated in the presence of APC between monoclonal antibodies anti CD3/CD28, and the growth factor IL-2, and its growth increases within a few weeks. Earlier, the beads were removed from the T cells by magnetic separation [33]. The T cell is incubated with the viral vector and, after a few days, the vector is washed out. This viral vector induces genetic material in the T cell, which later turns into a chimeric antigen T cell. Finally, CAR T cells are manufactured in bioreactor devices on a large scale.

3. Present Circumstance of CAR Therapy

Lately health technology is growing up day by day with push ahead world. Still

now in this antediluvian world those critical disease was coming cancer is one of them. Though many scientists try to bring out from this critical disease by severe methods and therapy in beginning of illness. This anti-cancer treatment proved as arresting invention within those treatments are established to cure. By this prodigious immunotherapy a satisfied number of cancer type treated such as R/R multiple myeloma, R/R large B cell cancer, diffuse large B cell lymphoma, R/R mantle cell lymphoma, B cell ALL, non-Hodgkin, R/R multiple myeloma, R/R follicular lymphoma. Against different kinds of tumor through this therapy proved 30% to 70% or greater than 90% potency. As much CTL019 a drug of CAR T therapy manufactured by Novartis that complete remission (CR) rate is 93%. At present clinical trials of this immunotherapy rise abruptly in the global [34].

Record of clinical Trials.gov showed 836 clinical studies (**Figure 3**) are running currently on CAR T cell therapy in worldwide till 8th November, 2021.By US FDA (food and drug administration) till November, 2021 got approval five therapy of CAR T cell those are listed in **Table 2** including their indications, yield institution and approval date.

Also exhibited in **Figure 4** the OR rate and CR rate on clinical trials by each approved CAR therapy. There has a relation between some others disease along Covid-19 (listed in **Figure 5**) and CAR T cell such as allergic reaction exposed on mast cell including basophil, eosinophil while IgE bind with FcsRI receptor that can release inflammatory mediators' results in type 1 hypersensitivity [26].

Ads (allergic disease) caused by IgE derived from B cells that may target of this artificial T cells. Regulatory T cells (Tregs) able to control asthma with

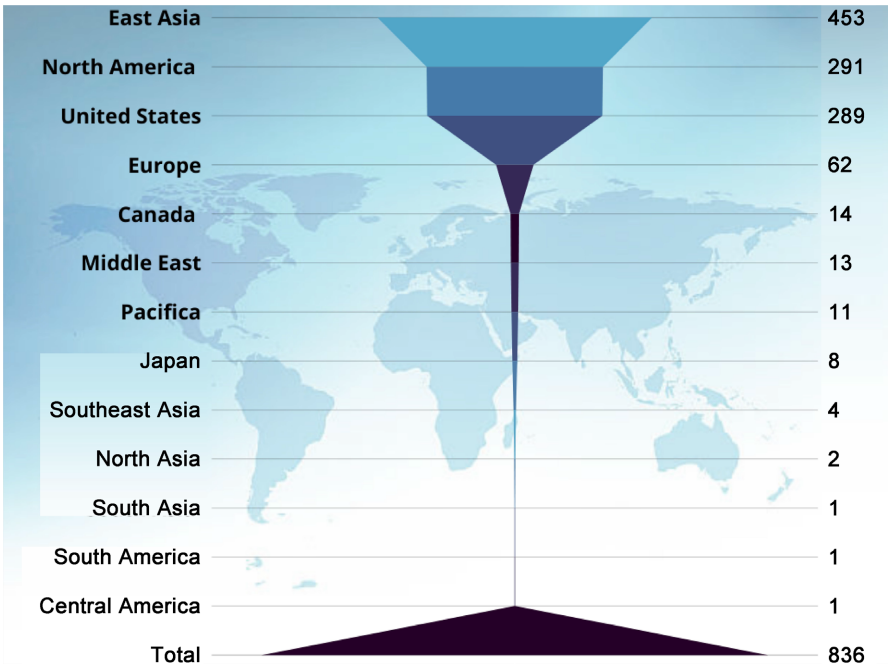

Figure 3. Funnel graph on number of clinical studies about CAR T cell by worldwide [40].

Table 2. List of currently existed CAR T therapy by FDA.

Brand Name	Kymirah	Breyanzi	Yescarta	Abecma	Tecartus	Reference
Proper Name	Tisagenlecleucel	Lisocabtagene maraleucel	Axicabtagene ciloleucel	Idecabtagene vicleucel	Brexucabtagene autoleucel	[41]
Approval Date	1st May, 2018	5th February, 2021	5th March, 2021	26th March, 2021	1st October, 2021	
Manufacturer	Novartis Pharmaceuticals	Juno Therapeutics Inc.	Kite Pharma Inc.	Celgene Corporation	Kite Pharma Inc.	
Indication	1. Young and pediatric adult patient (3 - 25) years with B cell precursor ALL 2. Adult patient with R/R large B cell lymphoma	1. Elderly patient with R/R large B cell lymphoma 2. Diffuse large B cell lymphoma	1. Old patient with R/R follicular lymphoma after two or more lines of systemic therapy	1. Geriatric patient with R/R multiple myeloma	1. Adult patient with R/R B cell precursor ALL 2. R/R MCL	

Abbreviation: R/R = Relapsed or Refractory, ALL = Acute Lymphoblastic Leukemia, MCL = Mantle Cell Lymphoma.

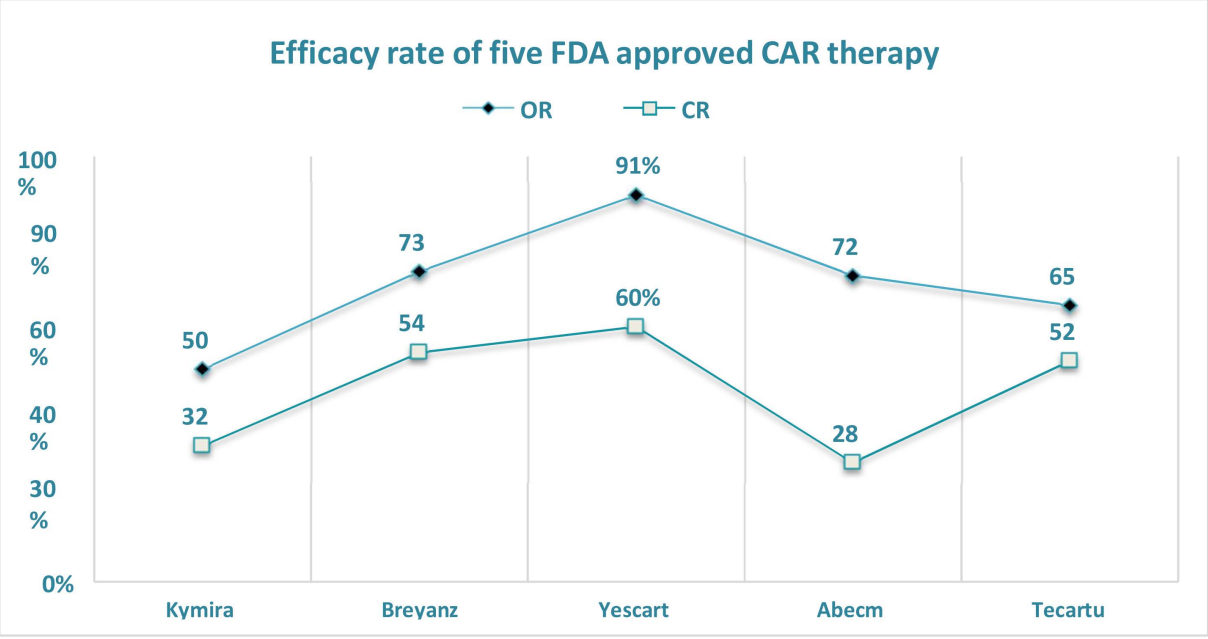

Figure 4. Efficacy rate of five approved CAR therapy [41].

hypersensitivity that influenced by Th2 immune response [30]. To cure infectious disease CAR T cells constructs enchanting such as CD8+ efficient to remove antigens [35]. Cytotoxicity of CD8+ also proved its potency against infection caused by HIV-1. Consequently, CAR T cells used to treat HIV-1 and gives wonderful trace in HIV-1 treatment beyond oncology [36] [37]. Cardiac fibrosis is one condition of cardiac disease that have not any targeted treatment recently but an experiment on this re-designed T cell induced mice have cardiac fibrosis showed effective CAR T cell recognize FAP (fibroblast activation protein) and target on enabled heart fibroblast [38] [39].

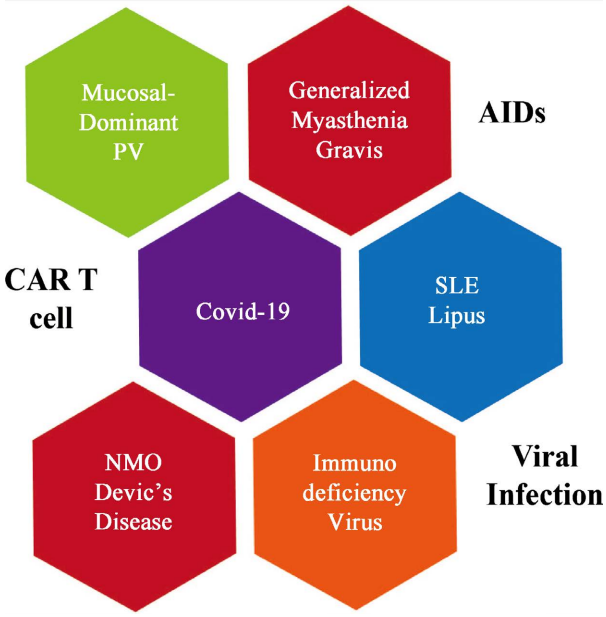

Figure 5. Relation between AIDs and viral infections with CAR T cells [2].

4. CAR T Cell Therapy for Hematological & Solid Malignancy

4.1. CAR T Cell Therapy

Genetically modified chimeric antigen receptor (CAR) T cell selects the target tumor antigen then binds to it and kills the tumor cell in perforin. As CAR T therapy, we first collect blood from the patient's body which is called leukapheresis then separate T cells from the blood. Later, by treating this T cell with a viral vector in the laboratory, we implant genetic materials in the T cell so that the receptors in the T cell grow. T cells containing this receptor are called Chimeric antigen receptor T cells. Next, we expand this generating CAR T cell then infuse this expanded CAR T cell into the patient's body. Finally, this CAR T cell receptor binds to the antigen on the surface of the cancer cell in the patient's body and kills the cancer cell. CAR T cell therapy is shown through **Figure 6**.

4.2. CAR-T Therapy for Hematological Malignancy

CAR-T cell immunotherapy is a significant treatment for hematological malignancies, which includes chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), lymphoma, multiple myeloma (MM) etc.

4.2.1. Acute Lymphoblastic Leukemia (ALL)

The effective CAR for the treatment of acute lymphoblastic leukemia (ALL) is CD19. According to one clinical trial report, CD-19 infusions per 16 patients resulted in a complete remission (CR) rate of 88% among 15 patients [43]. Where CR is a detectable disease indicator that works based on PCR. The same trial applied to children and adult B-ALL patients showed that the CR rate is 70% [44] [45]. For ALL patients CD19 is an ideal target for CAR therapy because CD22 is a potential target, but this treatment shows anti-CD19 deficiency in the

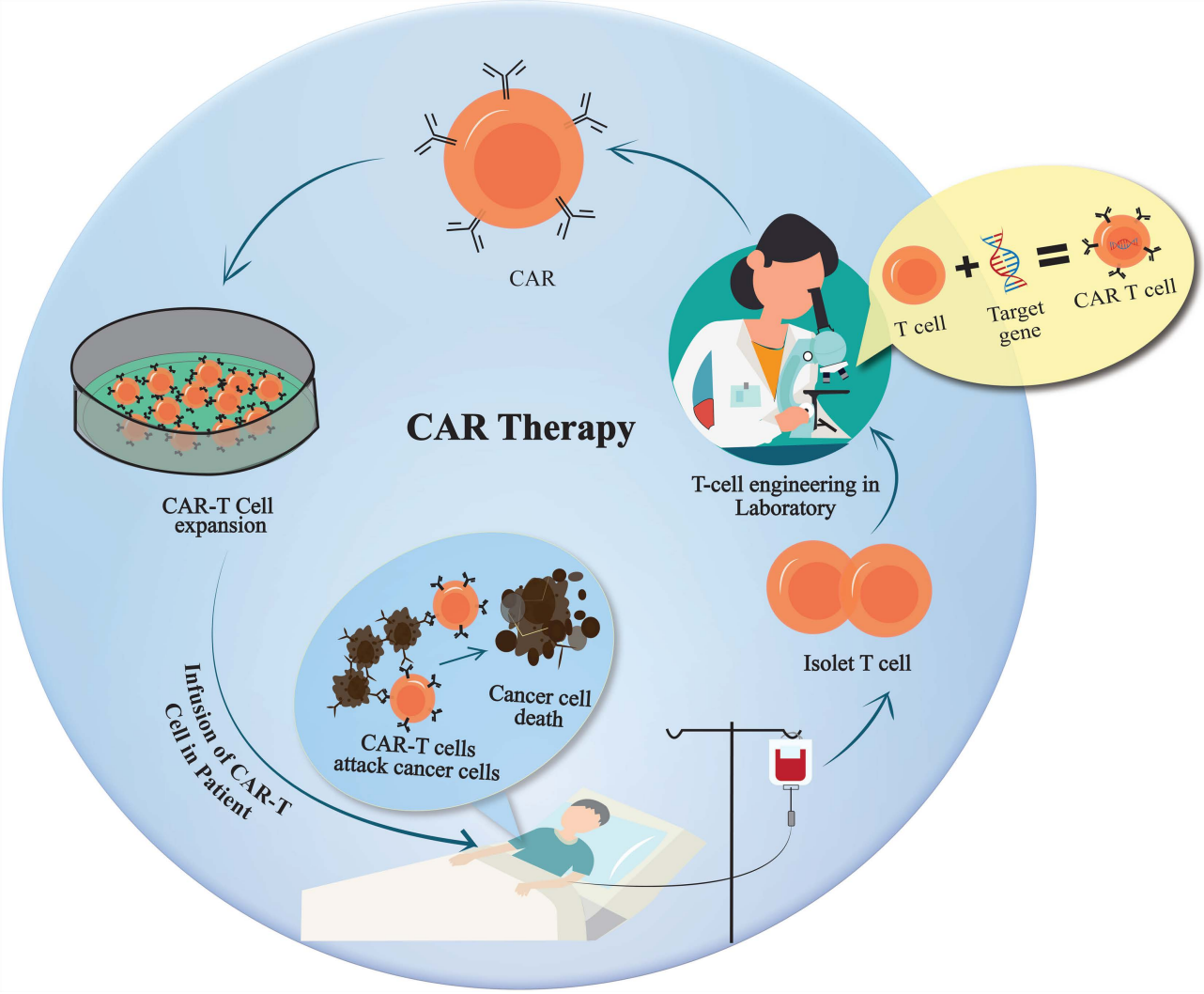

Figure 6. CAR T cell therapy [42].

patient's body, which diminishes the response of B cells in the patient's body [46] [47] [48].

4.2.2. Chronic Lymphocytic Leukemia (CLL)

It is one kind of blood cancer. On this, CLL patients have some CAR T effects. In patients with chronic lymphocytic leukemia (CLL), there is an early immune deficiency that results in T-cell expansion not being properly due to which CAR T therapy efficacy is limited in these patients. To overcome this problem, a drug called Ibrutinib is used, which inhibits the proliferation of b-cells, increases T cell expansion, and increases antitumor capability [1] [49]. Other studies have shown that CAR T therapy can be used in cases of b-cell malignancy in patients with allogenic hematopoietic stem cell transplantation, but in this case a side-effect called graft-versus-host disease is seen in the patient's body [50] [51].

4.2.3. CAR T Therapy in Multiple Myeloma (mm)

This multiple myeloma is derived from bone marrow. Updated taken by Criteria

for the Classification of Monoclonal Gammopathies, Multiple Myeloma and Related Disorders: A Report of the International Myeloma Working Group. Different types of treatment like autologous hematopoietic stem cell transplantation, chemotherapy, immune modulatory agents, etc. are not possible to treat this mm due to the abnormalities of myeloma cells [52] [53]. But according to some reports, CD19 has been shown to work on myeloma cells as well [54] [55]. But anti-CD19 may not play a vital role in myeloma cells, but it is harmful to more healthy tissue [56]. According to some clinical trials, CD138 CAR T cell therapy was used as the primary diagnostic marker in 5 multiple myeloma patients, resulting in stable condition in 4 patients, and in one patient, it was found that myeloma cells in the peripheral blood were reduced with advance plasma cell leukemia [57].

4.3. CAR T Cell Therapy for Solid Malignancy

In the case of solid malignancy, the next step in genetically modifying the T cell is to infuse it into the body. But, due to the presence of some barriers such as ineffective T cell trafficking, immunosuppressive microenvironment, T cell infiltration, etc., this CAR T treatment is still in the clinical phase in the field of solid malignancy.

4.3.1. Ineffective T Cell Trafficking

The presence of tumor-infiltrating lymphocytes (TIL) in the field of solid cancer patients indicates a positive clinical outcome [58] [59] [60] [61]. The better the antitumor response in the patient, the more cytotoxic T lymphocytes it has. There must be proper trafficking of cytotoxic T lymphocytes. CTL is a type of immune cell that kills different types of foreign cells, cancer cells. Some factors work in the field of proper CTL trafficking, like mismatching of chemokine-chemokine receptor pairs, down regulation of adhesion molecules, aberrant vascular etc. which act as the main barriers to CTL trafficking [62]. Proper chemokine production plays an important role in this. Proper chemokine production from the cell will enable CAR T cells to migrate to myeloma cells, so CAR T will be able to show its function on myeloma cells [63].

4.3.2. Immunosuppressive Microenvironment (IM)

Another barrier in the way of CAR T treatment in the field of solid malignancy is the tumor microenvironment. It is a key determinant of antitumor immunity with the capacity to inhibit the activation, infiltration, and effector activity of T cells. But immune suppressor, and some other obstacles like immunosuppression cytokines, inhibitory immune checkpoint which suppresses CAR T function from being present in the tumor microenvironment.

4.3.3. T Cell Infiltration

We use extracellular matrix, the main component of which is heparin sulfate proteoglycans (HSPGs), to help in the infiltration of T cells into the tumor microenvironment. HSPGs are produced by solid tumors, rather than by T cells

produced by stem cells in the body [64].

5. Result & Discussion

In treating malignant growths, CAR T cells have shown tremendous outcomes. But the therapy is still not optimal, because of the idea of the product, which is a "living medication," proposing its starting point (patient wellness) and quality. It is important to note that, to date, all CAR studies have, in any case, identified extreme grade 3 or 4 clinical AEs and passed. In the present survey, novel, imaginative ways to deal with managing the flexibility of CAR-T cells by consolidating rather than with exogenous pharmacologic medication (see **Table 3** for an outline) [65].

Table 3. A study of selecting for combining CAR-T cells and small molecules/drugs.

Years	CAR Target	Cancer/ Model	Small Molecule/Drug	Target	Statement	Ref.
Reversible spatio-temporal control of CAR						
2021	CD19	B ALL and lymphoma	Thalidomide analogs	C2H2, CRBN	ON-Switch: drug-dependent activity of antitumor and thalidomide analogues prevented spilt CAR dissociation. OFF-switch: inflammatory cytokine production is limited to retaining antitumor and thalidomide analogue induced CAR proteasomal deterioration.	[66]
2020	GD2	FAP^{+} Mesothelioma	Shield-1	LID domain-based CAR degradation	Induce drug-dependent CAR degradation and reduce CAR T cell activity temporarily.	[67]
2020	CD19	B ALL	ARV-771 or ARV-825 (retinol)	Bromodomain (BD of brd4)	Induce drug-dependent CAR degradation and reduce CAR T cell activity temporarily.	[68]
2020	PSMA	prostate	A-1155463, A-1331852 (BH3 mimetic)	LD3/Bcl-xL-based CAR dimerization	STOP-CAR: inactivate CAR T cell dynamically and reversibly.	[69]
2020	CD19	B ALL	A1120	hRBP4 and hRBP4 binders (RS3)	Drug-dependent regulation of CAR T cell activity.	[70]
2019	CD22	B ALL lymphoma	Asunaprevir	HCV NS3 protease	Switch-OFF CAR (SWIFF-CAR): proteolysis to constitutive CAR degron; dependent CAR degradation in Asunaprevir.	[71]
2019	CD19	B ALL	dasatinib	SRC kinases	Reversibly suppress CAR lymphocyte cytotoxicity, cytokine secretion and proliferation.	[72]
2019	CD19	B ALL lymphoma	dasatinib	SRC kinases	Reversibly suppress CAR lymphocyte cytotoxicity, cytokine secretion. and proliferation.	[73]
2018	CD19	$Cd19^{=}$ K562	ABT-737	Fab (AZ1) specific for Bcl-xL only in the attendance of ABT-737	CAR T cell activation is drug -dependent.	[74]

Continued

2017	PSCA, GD2, CD123	Prostate, melanoma, AML	AP1903(rimiducid)	FKBP/FRB-based dimerization of MyD88/CD40(iMC)	Intensify CAR therapy proliferation and activity of anti-tumor.	[75]
2015	CD19, MESO	CD19$^+$ or Meso$^+$ K562	Rapalog, (gibberellic acid)	FKBP/FRB-(or GID1/GAI)-based CAR dimerization	ON-switch CAR: Timing, location and dosages are controlled by CAR therapy activity and mitigate noxiousness.	[76]
Modulating CAR specificity						
2021	CD33, EGFR	AML, GBM	Methotrexate	Conditional scFvs	Decrease of CAR T cell affinity and cytotoxicity, reversible in drug-induced.	[77]
2018	HER-2, Axl, Meso	HER-2$^+$, Axl$^+$, Meso$^+$ K562	Soluble zipFv	Membrane-bound zipCAR	SUPRA-CAR: controls signaling, fine-tunes T cell activation, mitigates toxicity and allow multiple antigen sensing.	[78]
2016	5B9 epitope of La/SS-B	AML (others)	5B9-tagged anti-CD33 and anti-CD123 antibodies	CD33, CD123	Uni-CAR T (Universal): Redirect CAR in a time-and target-dependent manner; potent anti-AML activity.	[79]
2016	FITC	B ALL and lymphoma	FITC-modified anti-CD19 and anti-CD22 antibodies	CD19, CD22	Enable CAR-switch combinations; potent and dose-dependent antitumor activity.	[80]
Combinatorial anti-cancer approaches						
2020	CD19	B ALL	>500 small molecules	Multiple	Primary; birinapant, AT-406, LCL-161 (SMAC mimetics /inhibitor of apoptotic antagonists); Secondary: bryostatin-1 (PKC activator), idasanutlin and nutlin-3 (MDM2 inhibitors): Enhance CAR T cells cytotoxicity.	[81]
2020	CAIX	RCC (lung metastasis)	sunitinib	Multiple Kinases	Up-regulate CAIX in tumor cells; decrease MDSCs frequency.	[82]
2018	CD19	NHL	Suberoylanilide hydroxamic acid and LBH589; Celecoxib	Histone deacetylase; cyclo-oxygenase-2	Enhance CAR T cells cytotoxicity.	[83]
2018	FLT3	AML	crenolanib	FLT3 kinase	Synergize anti-leukemia effect.	[84]
2017	CD19	B ALL	Akt inhibitor VIII	Akt	Akt signaling inhibition during CAR T cell expansion improve antitumor efficacy.	[85]
2013	CD19	B ALL	ABT-737; ABT-263 (navitoclax)	Bcl-2 family members	Restore intrinsic apoptosis in tumor cells; Enhance CAR T cells efficacy.	[86]
2013	HER-2	HER-2$^+$ PD-1$^+$ tumor cells	Anti-PD-1 mAb	PD-1	Decrease MDSCs frequency; Enhance CAR T cell function.	[87]
2013	CD19	CLL	ibrutinib	Bruton's tyrosine kinases	Tumor clearance and mice survival and improved CAR T cells engraftment.	[49]

Continued

Mitigating the adverse effects						
2019	CD19	B ALL	lenzilumab	GM-CSF	Inhibit CRS and neurotoxicity.	[88]
2018	CD19	B lymphoma	anti-IL-6 and anti-IFN-γ mAb	IL-6 and IFN-γ	Reduce toxicity	[89]
2018	CD19, CD44v6	B ALL	anakinra, tocilzumab	IL-1 antagonist-receptor, IL-6	Inhibit CRS and neurotoxicity; extend leukemia-free survival.	[90]
2018	CD19	B ALL	anakinra; L-NIL and 1400W	IL-1 antagonist-receptor, iNOs inhibitors	Suppress CRS-related mortality by inhibiting macrophage-derived products (Nos, IL-1 and IL-6);	[91]
2018	CD19	B lymphoma	metyrosine	catecholamines	Keep mice safe from CRS lethal complication	[92]
2016	CD19	B ALL	Etanercept, infliximab	TNF-α	To reduce toxicity	[93]
Elimination of CAR T Cell						
2018	CD19	B ALL and lymphoma	AP20187, rapamycin	FKBP/FRB Inducible caspase 9 (rapaCasp9)	The *in vivo* process eliminates.	[94]
2017	CD19	B lymphoma	AP1903 (rimiducid)	FKBP/FRB Inducible caspase 9 (iCasp9)	CAR T cell eradication is extremely dose-dependent manner.	[95]
2014	GD2	N/A	rituximab	CD20 epitope fused to CD8 stalk (RQR8, also contain tCD34)	Enable CAR T cell selection, cell tracking (tCD34), and deletion (CD20).	[96]

The first apparent utility combines the effects of CAR therapy to sensitize tumor cells with drugs to further coordinate the effects of the two treatments. It demonstrates to the authorizing TME the strong tumor treatment mechanisms for relieving and non-prevention. This treatment also means more and often unexpected aspects, and patients will need careful observation and counseling during the effects and initial verification. Although it is elegant and able to protect patients from unwanted effects, it can be expensive and, when compared to patient-compatible CAR drug costs, may be a small amount of the total treatment cost [65].

To summarize the discussion, the combination of pharmacological drugs with CAR treatment is innovative and elegant. A personalized adaptation of the "living drug" will be an important step in improving the effectiveness of CAR therapy. The FDA and EMA approved those drugs, so they can easily be transferred to use in the clinic. Hopefully, future CAR/drug trials will show efficient clinical results in the near future [65].

*Just for the acknowledgment, stimulate, and signaling domains are depicted in order to grease the understanding. Fresh leader sequence, hinge/stalk, transmembrane domains, markers, and epitomes were removed when inapplicable. A rent (/) means that either one or further of the stimulate domains is present. N/A non-available. AML acute eyelid leukemia; B ALL precursor B acute lym-

phoid leukemia; Bcl-xL: Bcl extra-large; Bcl-2: B cell lymphoma 2; C2H2: Cys^2-His^2; CLL: chronic lymphoid leukemia; CAIX carbonic anhydrase IX; CRS cytokines release syndrome; CRBN: cerebelon; EGFR (epidermal growth factor receptor); FKBP: FK506 binding protein; FLT3: fms-like tyrosine kinase 3; FRB (FKBP-rapamycin-binding); GD2: disialoganglioside; GBM: globalism multiform; GM-CSF granulocyte-macrophage colony stimulating factor; HCV: Hepatitis C Virus; HER-2: epidermal growth factor receptor 2; hRBP4: human retinol retinal binding protein 4; IFN-γ: interferon gamma; iMC: ineducable MyD88/CD40; La/SS-B: human nuclear auto-antigen La/SS-B; LD3: human apolipoprotein E4 E; LID: ligand-induced dimerization; MDM2: mouse double minute 2 homolog; MDSC (myeloid-derived suppressor cells); Meso: mesothelin; NHL (non-Hodgkin lymphoma); Nos: nitric oxides; PD-1 (programmed cell death protein 1); PKC: protein kinase C; PSCA: prostate stem cell antigen; RCC: renal cell carcinoma; PSMA (prostate-specific membrane antigen); scFv: single-chain variable fragment; zip: leucine-zipper; SMAC (second mitochondria-derived activator of caspase); tCD34: truncated CD34; TNF-α (tumor necrosis factor alpha); tNGFR (truncated nerve growth factor receptor) [65].

6. Toxicity Management

Though CAR T cell therapy proved its powerful efficacy against various malignancies but this therapy also represents some toxicities during therapy as this is cellular product such as infusion reaction toxicities, tumor lysis, graft vs host, on target off tumor, on target on tumor, hypogammaglobulinemia. In this therapy identify, schism, and regulation of those toxicities is very fateful action to perfectly complete whole therapy. Different modes of action are responsible for toxicities of CAR T cell therapy. If this cell work on normal tissue instead of aimed cell then those normal tissue may be destroyed as anti CD19 responsible for gulp normal B cells [97] [98] [99]. Another reason of normal tissue spoil is that protein is not revealed on cancer cell suddenly cross interaction by CAR T cell [100] [101]. CAR T cell infusion may cause of TLS (tumor lysis syndrome) and acute anaphylaxis [1] [102] [103] [104] [105]. CRS (cytokine release syndrome) with morbidities including hypertension and fever is the salient and elaborately explained (**Figure 7**) toxicity by infusion of CAR T cells [43] [106]-[111]. This immunotherapy may causes of neurological toxicities while it run with CRS or without CRS [106] [107] [112]. Usually ruined which tissues exposed antigen and recognized by CAR. During progression of this T cells the mechanism is liable for toxicity that can be repress but not terminated because of entire search for targeted antigen that revealed on normal tissues.

6.1. Acute Systemic Inflammatory Syndrome or CRS

In this therapy it's a major enough dangerous adverse effect that treated by tisagenlecleucel is 77% [114] and 57% [115] gradually in patients who have NHL and ALL. In backward patient of NHL with CRS treated 93% by axicabtagene

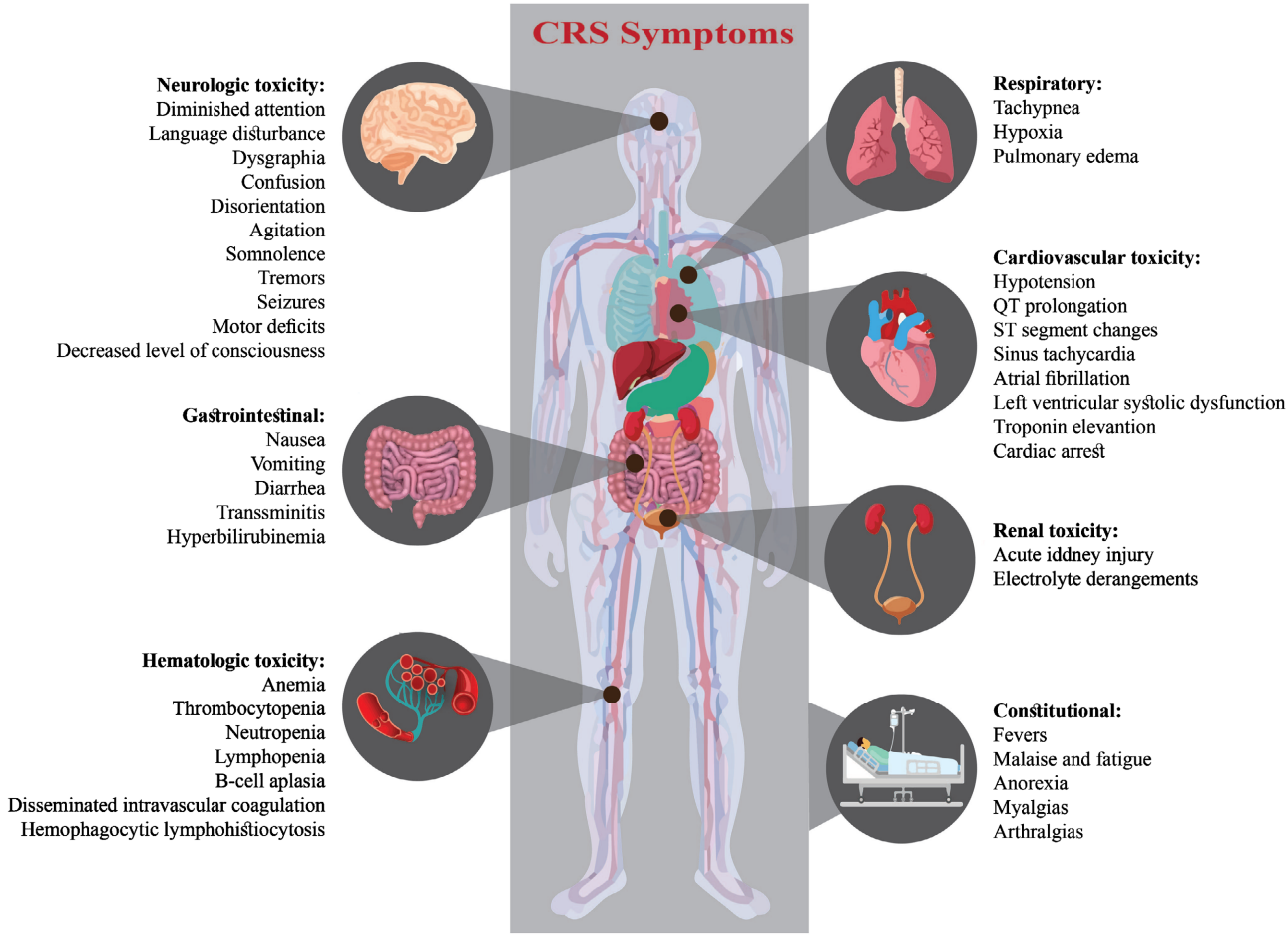

Figure 7. CRS symptoms by different organs of human body [113].

ciloleucil [116] Each grade of CRS has different symptoms and management system (**Figure 8**).

6.2. Neuropsychiatric Syndrome or ICANS

This kind of toxicity is another general side effect of CAR T cell therapy that's symptoms are very apparently connected to CAR product, patient age, disease condition and ICANS may occurred during CRS or individually [114] [117] [118]. ASTCT also appending ICANS into consensus based grading system to clinical experiment and regular use [117] with ICE (Immune effector cell encephalopathy) score, some general recommendation, symptoms of cerebral oedema. For ICANS managements or prevention there have no approved treatment though it can be controlled initially by some supportive cares (**Figure 9**).

7. CAR Combining with Oncolytic Virus Therapy

Along this startling immunotherapy some other materials of treatment may use and this kind of therapy mentioned as combinational system. Solid tumors treated by this combinatory CAR method without exposing any heterogenic effect and obviously it succeeds to increase therapeutic window of this chimeric

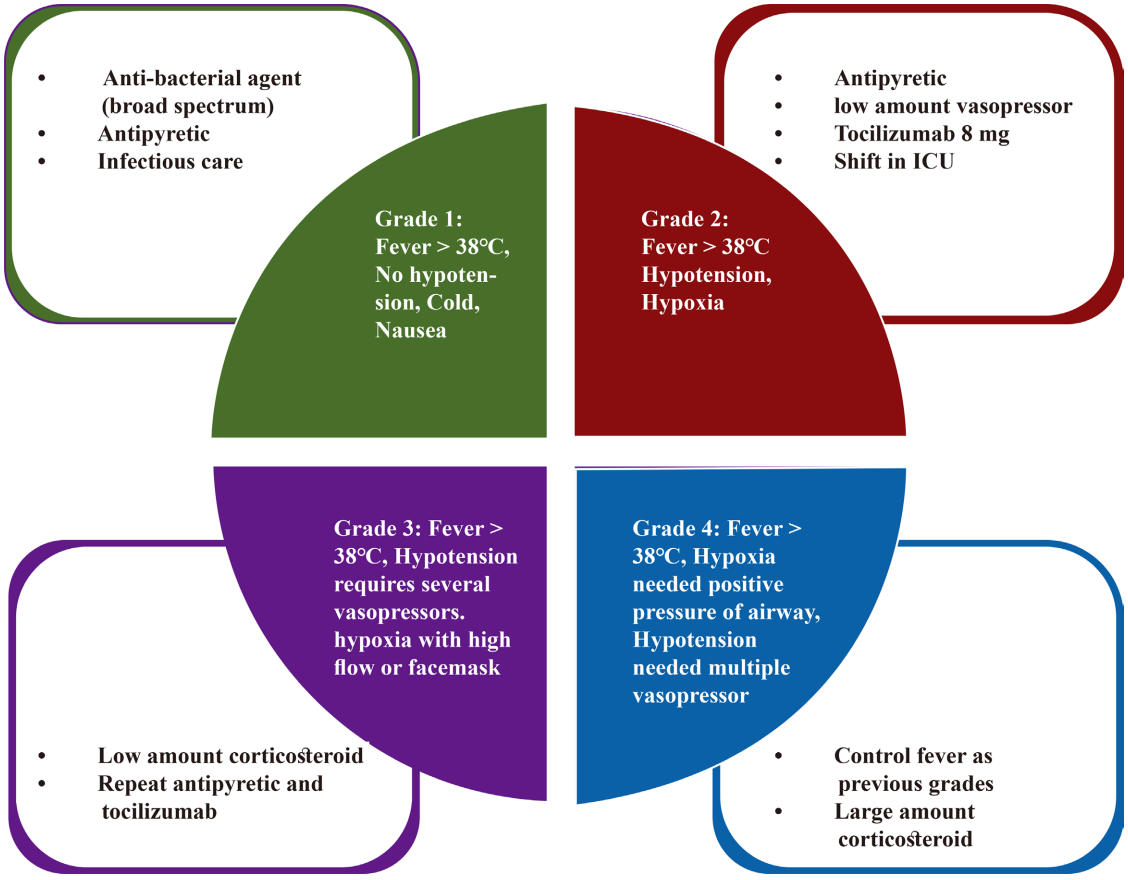

Figure 8. Symptoms and Management of CRS as Grading [113].

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7 - 9	3 - 6	0 - 2	Failed to perfrom
Manifestation	Seizure and cerebral oedema absent	Seizure and cerebral oedema absent	Though rapid resolution but focal and generalised seizure, local oedema on lumber puncturing without bleeding.	Life risked long duration of seizure, diffuse cerebral oedeme
Management	Continuous observation.	Dextroxethorphan if CRS>1 associated and tocilizuxab also.	Dextroxethorphan if CRS>1 associated and tocilizuxab also.	Methylprednisolone CRS>1 associated with also tocilizumab.

Figure 9. Symptoms and Management of ICANS grades [119].

antigen receptor T cell therapy. One clinical trial on OVs (oncolytic) viruses proved as a plight product for treatment of solid tumor and FDA approved GM-CSF against advanced malignant melanoma that able to express OHVs (oncolytic herpes virus) [120]. This oncolytic virus therapy capable to work on specific target and destroy malignant cells omitted normal tissue. During need to active immune system for given risky signals of carcinogenic cells these virus results in lysis of cancer tumors through deliver of virus lineage and expansion of virus inoculum [121]. Yet now many clinical studies either *in vitro* or *in vivo* drive to determine synergism between OVs and CAR cell that listed in **Table 5** Contemporary there may yield irrepressible synergic effect on CAR T cell while OVs engineered in such a way it pushes few immunomodulatory components to expose. But in case of better non-engineered OVs with CAR they may express different outcomes. Suchlike GD2 CAR T cell proliferation enhanced by HSV1716 in melanoma and rhabdomyosarcoma cancer [122]. By these experiments (**Table 4**) OVs therapy in single or combination recommended to curbed of tumor cell.

Table 4. Preclinical investigation of CAR combining with OVs.

OVs component	Target of CAR	Signaling domain of CAR	Cancer type	Quantity	Result	Ref
AdC68-TMC-Tcd19	CD19	CD3ζ + 4-1BB + CD28	Hepatic	4×10^6 CAR T and 8×10^6 OVs	Tumor decrease and outlive	[123]
rAd.sT	meso	CD3ζ + 4-1BB + CD28	Breast	1×10^7 meso CAR and 2.5×10^{10} OVs	Weight, volume and metastasis of tumor decrease	[124]
CAdTrio	HER2	CD3ζ + CD28	Skin	1×10^6 CAR and 10^8 OVs	Tumor volume decrease and better condition	[125]
mCD19VV	CD19	CD3ζ + CD28	Melano-ma skin	1×10^7 CAR and 10^8 OVs	Tumor volume decrease	[123]
OV19t	CD19	CD3ζ + 4-1BB	Breast	10^7 OVs and 5×10^6 CAR T	Decrease of tumor volume	[126]
IL-2	meso	CD3ζ + 4-1BB	PDAC	1×10^9 Onc.Ad and 5×10^6 CAR T	Tumor growth and metastasis reduce	[127]
Onc.Ad-EGFR BiTE	FR-a	CD3ζ + ICOS	PDAC or CRC	1×10^7 CAR and 10^9 OVs	Reduce tumor growth	[128]
VV. CXCL-11	meso	CD3ζ + 4-1BB	Lung	10^8 OVs and 1×10^7 CAR	Tumor volume consumes	[129]
CAdVEC-aPDL1	HER2	CD3ζ + CD28	Skin and Prostate	1×10^6 CAR and 10^7 OVs	Suppress of tumor volume	[130]
aPDL1	HER2	CD3ζ + CD28	Head and neck skin cancer	1×10^6 CAR and 10^8 OVs	Tumor metastasis and growth consumes	[131]
IL-15	Ganglio-side GD2	CD28 + OX40	Neurobl-stoma	1×10^7 CAR and 10^9 OVs	Tumor growth decrease	[132]
EphA2-TEA-VV	HER2	CD3ζ + CD28	Lung	1×10^7 CAR and 10^9 OVs	Survival and tumor growth reduce	[122]

8. Commercialization of CAR-T Cell

FDA-supported items are monetarily accessible for authorized signs altogether and DLBCL there is a quickly developing business in conveying CAR-T cell. CAR T cells are reasonable to expect to be that this extensive monetary motivating force is adding to current publicity concerning this treatment. Biotechnology organizations have drawn in interest in the request for billions of US dollars on the premise that CAR-T cell items will be industrially fruitful, yet this ought not to occupy from a target appraisal of the proof on which we base treatment choices. In the event that this treatment does satisfy its prospects, a political discussion will be required concerning admittance to therapeutic medicines either being an advantage for the rich or an appropriate for those out of luck [133].

The tailor-made assembling processes presently utilized for profoundly customized designed T cell treatments bring about significantly expenses. The expense of manufacturing Car T cells is relied upon to diminish. A point-by-point examination of the general wellbeing consideration of the evaluation of quality changed cells is past the extent of this analysis. However, some factors have as of late been summed up [30].

9. Application of CAR T Cell Therapy

The treatment methods of CAR-T cell therapy that are being used to treat cancer and in various clinical trials include hematological malignancies, which include ALL; acute lymphoblastic leukemia, CLL; chronic lymphoblastic leukemia, lymphoma and MM; multiple myeloma. Also, application of CAR therapy research development plan and development is underway for myeloma, sarcoma and breast cancer treatment which includes solid tumors. The use of CAR-T cell immunotherapy in the context of advances in the treatment of various cancers and its practical success is as follows: The use of CAR-T cell therapy in various clinical trials to treat ALL, CLL and its outcome is shown in **Figure 10** and also treat MM, Lymphoma, solid tumor in various clinical trials their antigen uses or data information summarized in **Tables 5-9**.

9.1. CAR T Cell Therapy for ALL (Acute Lymphoblastic Leukemia)

Table 5. Effects of CAR therapy on ALL through selected clinical trials.

CAR Antigen	Institute	Sample		Participants Effective Number	Year of Publishing	Ref.
		Number (M/F)	Age			
CD19 2nd 4-1BB	University of Pennsylvania	30 (18/12)	Children and Adult	30	2014	[47] [98]
CD19 2nd 4-1BB	Fred Hutchinson Cancer Research Center	29	Unavailable	26	2015	[134]
CD19 2nd 4-1BB	University of Pennsylvania	27[a]	Adult	27	2016	[1]
CD19 2nd 4-1BB	Hebei Yanda Lu Daopei Hospital	42 (28/14)[b]	Children and adult	40[c]	2017	[135]

9.2. CAR-T Cell Therapy for CLL (Chronic Lymphocytic Leukemia)

Table 6. Effects of CAR therapy on CLL through selected clinical trials.

CAR Antigen	Institute	Sample		Participants Effective Number	Year of Publishing	Ref.
		Number (M/F)	Age			
CD19 2nd CD28	National Cancer Institute	15[d] (8/7)	51.67 ± 11.22	15[d]	2014	[114]
CD19 2nd 4-1BB	University of Pennsylvania	14 (12/2)	66.90 ± 8.10	14	2015	[1] [136]
CD19 2nd CD28	National Cancer Institute	20 (11/9)	50.93 ± 12.86	20[e]	2016	[136]
CD19 3rd CD28/4-1BB	Fred Hutchinson Cancer Research Center	24[f]	59.54 ± 7.87	24	2017	[137]

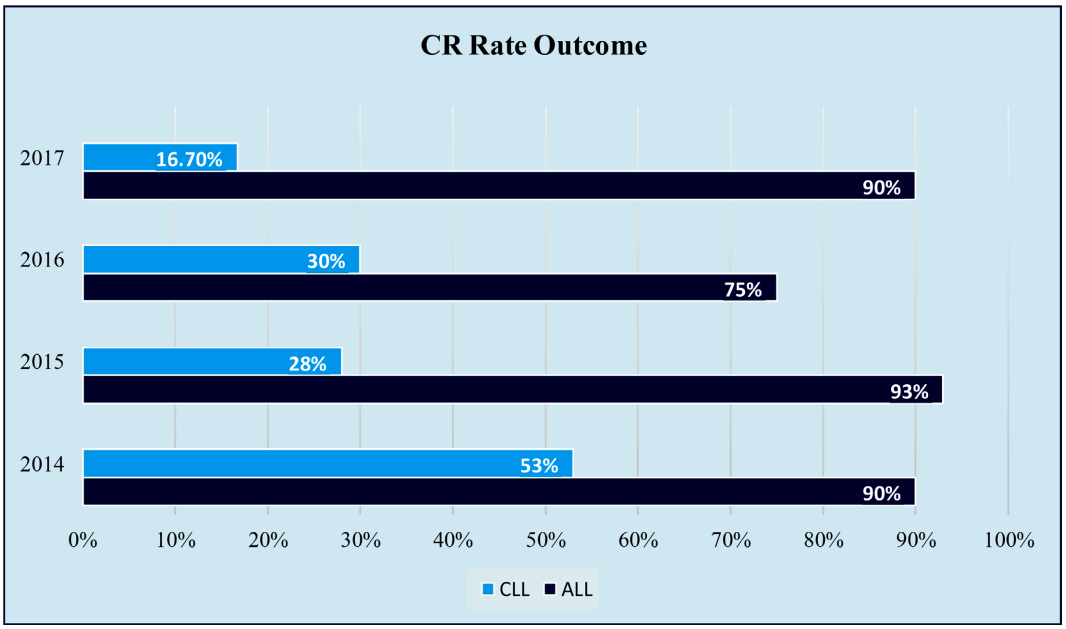

Figure 10. Outcomes of CR (Complete Remission) rate in CLL (chronic lymphocytic leukemia) and ALL (acute lymphoblastic leukemia) obtained by clinical trials using certain CAR antigens selected at different institutes [112].

9.3. CAR-T Cell Therapy for Lymphoma

Table 7. Effects of CAR therapy on Lymphoma through selected clinical trials.

CAR Antigen	Institute	Sample		Participants Effective Number	Outcome	Year of Publishing	Ref.
		Number (M/F)	Age				
CD19 2nd CD28	National Cancer Institute	15[g] (8/7)	51.67 ± 11.22	15[g]	Rate of CR: 53%; Rate of PR: 26%;	2014	[112]
CD19 (the generation is unknown)	Fred Hutchinson cancer Research	28 h, f	Adult	24 [i]	8.3% and PR rate is 41.7%; Addition of fludarabine received in 16 patients. lymphodepletion, the rate of CR is 42% and PR rate is 25%.	2015	[138]
CD30 2nd 4-1BB	Chinese PLA general Hospital	18 (13/5)	31	18	PR rate: 39%; SD rate: 33%	2016	[139]

9.4. CAR-T Cell Therapy for MM (Multiple Myeloma)

Table 8. Effects of CAR therapy on MM through selected clinical trials.

CAR Antigen	Institute	Sample		Participants Effective Number	Outcome	Year of Publishing	Ref.
		Number (M/F)	Age				
CD138 2nd 4-1BB	Chinese PLA general Hospital	5 (1/4)	Adult	5	4SD[j]	2015	[57]
BCMA 2nd 4-1BB	University of Pennsylvania	11[f]		6k	1CR; 1PR; 1SD	2016	[140]
BCMA 2nd 4-1BB (bb2121)	Bluebird Bio	9[f]		9	2CRs in a cohort of 15 * 10^7 CAR-T cells; 1PR in a cohort of 5.0 * 10^7 CAR-T cell, 1PR in the cohort of 15 * 10^7 CAR-T cells and 2PR in a cohort of 45 * 10^7 CAR-T cell; 1SD in the cohort of 5.0 * 10^7 CAR-T cell and another is the cohort of 45 * 10^7 CAR-T cell.	2017	[141]

Abbreviations: ALL (acute lymphoblastic leukemia); CAR t cell (chimeric antigen receptor T cell); BCMA (B cell maturation antigen); MM (multiple myeloma); CR (complete remission); M/F (male and female); PR (partial remission); Ref (reference); SD (stable disease); CLL (chronic lymphocytic leukemia); [a]The calculation is the total number of samples. [b]In the trials has two groups; one contains 42 primary refractory/hematological relapsed and 9 refractory minimal residual disease by flow cytometry patients of B-ALL. [c]In the trial two patients died from related treatment mortality. [d]4 CLL patients are including. [e]There are CLL patients 8. [f]No gender indicated. [g]There are 11 lymphoma patients. [h]In this clinical trial has two main groups, one is NHL (non-Hodgkin lymphoma) and the other one is CLL (chronic lymphocytic leukemia). [i]There are 4 patients were not available, among which 2 died. [j]This study apply the accurate value instead of rate, where the response rate is meaningless (sample size is less than 10). [k]Because of screen fail (n = 2); five patients are not receiving treatment, rapid MM progression/renal failure (n = 2), self-choice (n = 1). Age of patients are expressed ± mean standard error of mean and whether the data are available [42].

9.5. CAR-T Cell Therapy for Solid Tumors

Table 9. The application of some CAR antigen on different solid tumors.

Antigen	Cancer	Effectiveness	Ref
MUC16 (Mucin 16)	Ovarian Cancer	reported as a potential target for treatment of ovarian cancer.	[142]
Mesothelin	Breast cancer	Promising immunotherapy for breast cancer treatment.	[143]
Prostate-specific membrane antigen (PSMA)	Prostate Cancer	efficacy and safety for prostate cancer treatment.	[144]
Carbonic anhydrase IX (CAIX)	Renal Cancer	The first generation of renal carcinoma cells to be associate with cytotoxic function in high degree cytokine secretion.	[143]
IL-12	Gastric Cancer	A significant improvement in ICAM 1^{high} advanced gastric cancer patients.	[145]
Prostate stem cell antigen (PSCA), Mucin-1	Lung Cancer	which can lead to the desired therapeutic outcome in lung cancer.	[146]
Glypican-3 (GPC3)	Liver Cancer	promising a useful method for the treatment of malignancies.	[147]
Doublecortin-like kinase 1 (DCLK1)	Colorectal Cancer	It effectively eradicates primary and metastatic colon cancer cells.	[148]

10. Future Opportunity

The initiatory advancement of CAR-T cell immunotherapy treatments has concentrated amazingly on ALL, commonplace cancers in young people. Over 80% of kids are determined to have ALL that emerges in B cells. The dominating kind of pediatric ALL will be restored by serious chemotherapy therefore patients whose diseases return after chemotherapy or a foundational microorganism relocates, treatment choices are few and far between.

CAR-T cells have made significant progress in the treatment of hematological malignancies in recent years. However, it is still in the development stage and more advanced quality measures are being taken to prevent CRS with various adverse and side effects arising after providing CAR medical service to patients [42]. A review revealed that a bivalent tandem CAR (TanCAR) was intended to intervene in the bispecific initiation of immune system microorganisms [149]. And also proposed that tandem CAR (TanCAR) reactivated T cells against two unique antigens. Also, TanCAR delivered a synergistic improvement in T lymphocyte enactment [149]. Treatment for malignity in hematology, which might be possible Besides, with the advancement of universal CAR immunotherapy for hematological malignancies treatment, which can stay away from the issue that autologous T lymphocytes of patients are hard to acquire and diminish the expense of treatment, and then conjecture that the use of CRISPER innovation to alter allogeneic qualities gives potential to the progress of uniCAR T cell treatment [150]. Another technique called the "suicide gene system" is likewise commendable and merits consideration [151]. Artificially incited iCas9 dimerization is quite possibly the most noticeable self-destruction gene in lymphocytes based on immunotherapy, which has shown exceptional proficiency in clinical preliminaries of patients [152]. As a general rule, these treatments may stay away from the unfriendly occasions brought about via CAR-T cell immunotherapy for optional medication for cancer treatment, which additionally shows a new opportunity for the future [150].

11. Conclusion

Chimeric antigen receptor T cells are creating the conversion from simply "favorable" to being "fruitful" for hematological virulence's treatment. As we pursue to improve the ability of CAR T cells immunotherapy, that expresses chimeric tumor-targeting receptors and allows them to target in the lump micro-environment. We can anticipate broader application beyond hematological carcinomas and into solid tumors. With rising interest in the sphere from profit-oriented entities, we are optimistic that the evolution and clinical execution of this sensational perspective will now hasten.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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