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A COMPREHENSIVE REVIEW ON: CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY IN CANCER TREATMENT

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Abstract

Chimeric antigen receptor T-cells or CAR T-cell therapy is a newly discovered method that has shown great promise for the global patient population to cure cancer. Chimeric antigen receptor T-cells are generally prepared by removing T-cells from the patients' blood and modifying them using genetic engineering, to express a Chimeric Antigen Receptor on their surface. The studies done so far have shown its major effectiveness against Beta-cell malignancy, ovarian carcinoma, and lymphoblastic leukemia. The therapy can cause Cytokine Release Syndrome, neurotoxicity syndrome, tumor lysis, etc. as its major adverse event. But recent improvements in the therapy has proved that these adverse events can be effectively minimized to a great extent. The future of CAR T-cell therapy is very promising and is expected to fulfil all global regulatory requirements as well as overcome any manufacturing and toxicological obstacles and become available for a large number of populations. This review is based on the overall prospects of CAR T-cell therapy, the major toxicity related problems, and the prospect of this therapy.

Keywords: Chimeric Antigen receptor (CAR) T-cells; Adoptive T-cell transfer (ACT); Solid tumor therapy; Lymphoblastic leukemia; CAR T-cell toxicity; β-cell malignancy

Introduction:

In the present world cancer is one of the greatest threats to our society. Medical science is straining every nerve to abolish this threat. Many fruitful and hopeful results have also come up. Sometimes these newest therapies/ treatments are yielding miraculous results. Adoptive T-cell transfer (ACT) is one of them. It is a type of therapy that depends upon transfusion. The principle of the therapy is the infusion of different types of T-Cells to kill the malignant cells as well as prevent re-occurrence [20]. Three major forms of ACTs are currently being developed for the treatment of cancer; these ACTs are: **A.** CAR T-cells **B.** T-cell receptor (TCR) T cells and**C.**Tumor-infiltrating lymphocytes (TILs)[2].

CAR T-cells therapy is a surprising andworthwhile treatment procedure in cancer (mainly human lymphoblastic leukemia), and with some supportive care it has lesser life risk[69, 70]. The patients at high risk with Philadelphia chromosome-positive disease [22] as well as those with the relapsed disease has shown great response to this therapy. The T-cells are genetically engineered either retrovirally or lentivirally, to express the tumor-targeting receptor.These receptors are the chimera of a signaling domain of the T cell receptor (TcR) complex and an antigen recognition domain such a single-chain fragment of an antibody, known as Chimeric Antigen Receptor (CAR) T-cells [1].

To understand the current scenario of this therapy the main focus should be on:

(1) Use of CAR T cell therapy in solid tumors and human lymphomas
(2) The overall prospect of this therapy
(3) Adverse effects related to CAR T cell therapy and their management
(4) Prospect of this treatment procedure in the future.

Boon Of CAR T-Cell Therapy On B-Cell Malignancy:

There are miscellaneous groups of cancerous conditions that are derived from β-cells and surrounded by B cell malignancies. For an example, pre- β acute lymphoblastic leukemia (pre-B-ALL) derives from progenitor cells at the pre-B-cell developmental phase in the bone marrow, while diffuse large B-cell lymphoma (DLBCL) derives from B-cells present in the germinal centers of lymphoid tissues[1]. On the other hand, blood, bone marrow, and lymphoid tissues contain mature phenotype B cells and tumor cells in the case of chronic lymphocytic leukemia [1]. CD 19 and CD 20 are the antibody targeting molecules for B lineage acute leukemias [23]. CD 19 is a better antibody targeting molecule for B lineage acute leukemias than CD 20. Some

clinical trials have shown that the CAR T cells which target CD19[42], exhibited significant results. There are some membrane-bound antibodies that acts as another B cell target and for this reason, nowadays development of CAR T cells is done for targeting Ig κ or λ chain [2].

Immunotherapy is very effective for patients with B-cell malignancy. According to the existing research outcomes, it is evident that that genetically engineered CAR T-cells can target CD 19 have shown remarkable results in B cell malignancy [1, 10, 67, 68]. According to immunology, T-cells under suitable physiological conditions have the ability to survive, expand, and can kill the neoplastic cells. Cancer has the ability to evolve and evade from different treatments and this is where CAR T-cell show significant of sustained cytotoxicity by proliferating *in-vivo* and they can reach one tumor cell from another, whereas in general single antibody can affect one tumor cell without proliferation. Complete responses and different transient partial responses are already found in several trials [1, 71].

Conventional T cells are known to have an outstanding ability to differentiate between foreign peptide-MHC (pMHC) and self pMHC through their TCR [8]. An antigen that can recognize the extracellular domain and an intracellular signalling domain is present in the design of a CAR molecule. The extracellular domain consists of a cell surface antigen, while the intracellular domain consists of merged signalling domains from the TcR complex and costimulatory proteins. The second-generation CAR has a signalling domain from a costimulatory molecule [1].

Role Of CAR T-Cell Therapy In Solid Tumors:

Neo-antigensare generally newly formed antigens on the surface of solid tumor cells resulting from altered tumor proteins caused by mutations or in some cases viral proteins as well. They were considered as a target for CAR-T therapy as their expression is known to be restricted to tumor cells [24]. But it is now established that being a result of tumor-specific mutations most neo-antigens are highly individualized and therefore not practical for CAR therapy. But in recent studies, numerous neo-epitopes have been identified and they are found to be more generalized and targetable [12]. In the case of ovarian carcinomas overexpression of a glycoprotein known as MUC16 can be observed. Car-T cell is now reported to successfully target these glycoproteins[43].

Foreign particles after entering cells undergo breakdown to form peptides which are then brought to the surface by proteins known as Major histocompatibility complex or MHC and then presented to T-cells [25]. As all the nucleated cells in our body have these MHC molecules, the CAR-T cells are engineered to show selective affinity towards certain MHC bound antigens. T-cells that are restricted to MHC class-I are theoretically known to be specific towards tumors and are considered as capable of direct recognition of many types of tumor cells. However, downregulation of Major Histocompatibility Complex class I molecules is often seen in the neoplastic cells or tumor cells making them an unstable target. Competent Antigen-presenting cells undergo a mechanism called Cross-priming and produce exogenous antigens and initiate them to the T-cells[66].

Such indirect recognition of antigens associated with thetumor by T cells can result in an effective means of targeting tumor masses that have lost MHC expression by triggering innate immunity or the non-specific defense mechanism and vascular collapse [13].

T cells hold up to the situations where the target antigens are evident and can produce cytokines, chemokines, and anti-angiogenic factors.They can affect the growth of the tumorby suppressing the proliferation of tumor cells. They can prevent the apoptosis of the tumor cells as well [41]. T cells that mediate effective antitumor responses may also directly mediate cytotoxic responses against tumor cells, either through their expression of apoptosis-inducing molecules or through the release of cytotoxic granules[13].

Adverse reactions of CAR T cell therapy:

A surface receptor is present in the CAR T cell and the chimeric molecule is build up with an extracellular domain obtained from a β-cell which is linked with an intracellular T cell which can signal domain by a transmembrane sequence. Recent studies have shown that the frequent toxic effects of CAR T-cell therapy are cytokine release syndrome (CRS) [26] and immune effector cell-associated neurotoxicity syndrome (ICANS)[44], at past which was called as cell-related encephalopathy syndrome. There are other adverse effects observed followed by the infusion of CAR T cells and must be kept in mind in case of clinical practice.

There are some laboratory practices to be followed to monitor CAR T-cell toxicity. Though the CAR T-cell infusion procedure was found safe in many cases,there are some precautious procedures which are to be carried out. Acetaminophen and diphenhydramine are to be administered at least 30 minutes to 1 hour[27] [28]before CAR T cell infusion as premedication to minimize toxicity. Especially, the systemic use of corticosteroids as prophylactic can hamper the activities of CAR T cells and therefore it shouldbe avoided during therapy, but it is effective in case of severe toxicity resulting from the T-cell therapy due to its immunosuppressive properties [45]. Important symptoms like body temperature, rate of respiration, pulse rate, blood pressure, and pulse oximetry are used to measure oxygen saturation previously, during the procedure, and after infusion in a short interval. The availability of emergency drugs and equipments must be

available to overcome emergency conditions during and after the procedure [14].

After the completion of the infusion of CAR T cells, the patient needs thorough check-up because that patient remains at high risk of cytokine release syndrome and neurotoxicity syndrome

Cytokine release syndrome or CRS:

CRS is the major and common adverse effect that usually occurs after CAR T-cell therapy. There are two main steps that describes the total process of occurrence of cytokine release syndrome as a result of the infusion of CAR T- cells. In the first step, the activation and expansion of CAR T-cells occur because of the interaction between the CAR T-cells and its targets. As a result, both the tumor cells and normal cells are affected and activation of immune and non-immune cells occurs resulting in a massive release of cytokines. Mostly the released cytokines consist of IL-6, IL10 & Interferon –Y [46]. Interferon–Y, later on, induces activation of further immune cells and macrophages. These macrophages results in the release of additional cytokines [47]. In the second case, the combined signalling factors act by pushing towards the activation of monocytes and macrophages which enhance the tumoricidal property [14]. Cytokine release syndrome occurs with some variations of symptoms starting from prodromal syndrome to life-threatening conditions. The starting symptoms of cytokine release syndrome move forward with a flu like syndrome like fever, headache, fatigue, arthralgia, malaise and myalgia, etc.[46] The first clinical sign of cytokine release syndrome is pyrexia or hyperthermia (the body temperature rises above 38°C), in some cases, the body temperature rises above 40°C. In comparison with patients suffering from mild cytokine release syndrome to the patients with severe cytokine release syndrome fever peaks earlier and lasts longer in case of severe CRS [48]. According to some clinical practices, severe CRS occurs followed by the hemodynamic stability and dysfunction of some organs successively mild to moderate hypoxia and hypotension can also occur[14]. But in the circumstances of haematological malignancies the patients in mostcases who givea positive response to CAR T-cell therapy, suffer from mild to moderate CRS due to its infusion [7].

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.0) contains a grading system that is followed to manage CRS which is carried out depending upon signs and syndromes[49]. Apart from it, PENN/CHOP is also widely a used gradation system to monitor CRS and to treat CRS after CAR T infusion[14]. While they both include a four-level scale of severity, there are some differences. So recently to resolve this issue a harmonized grading system is formed by theAmerican Society for Transplantation and Cellular Therapy[50].When the symptoms of early-stage CRS start to reveal, the patient should be kept on observation and they should be provided with symptomatic treatment with drugs from antipyretics and/or analgesic category and NSAIDs should always be avoided, which could be harmful to renal functions [16]. Additionally, in the case of febrile patients,the infection should be excluded and in the case of patients suffering from neutropenia, empiric antibiotics should be given [14]. Usually, prophylactic antibiotics are not used. The other side effects of CRS can be overcome by using antiemetic drugs, oxygen, I.V. fluids, and/or the required dosage of vasopressors. But corticosteroids must be avoided.

Severe CRS (sCRS), ≥ Grade 3 by Penn grading system with relapsed B-ALL are treated withtisagenlecleucel[51] andpatients with relapsed/refractory DLBCL treated with axicabtageneciloleucel and tisagenlecleucel, respectively[14]. An FDA approved known IL-6 receptor antagonist is Tocilizumab (Roche) and it is being used in case of management of severe CRS. The patients having sCRS has already demonstrated a high response rate by its use [14, 51].

Neurotoxicity Syndrome:

According to the existing research works, neurological toxicities are related to increased levels of serum cytokine. Increased cytokine levels lead to a significant change in motor activity and impact neuro-circuits in the brain. Previouslyit was assumed that the pathogenesis of neurotoxicity is related to direct parenchymal CAR T-cell toxicity, though it is not clear, in current studies, the dysfunction of B-B-Barrier (Blood-Brain-Barrier) is considered as the ultimate factor of neurotoxicity [14, 52-54]. According to normal human physiology, in the structure of B-B-Barrier, endothelial cells are presently surrounded by basal lamina, pericytes, microglia, and astrocytes. Additionally, the disablement of B-B-Barrier function relates to some factors like TNF-alfa, IL-6, IL-1, and angiotensin-1, and angiotensin-2[17-19]. Except for these, there are some molecules like macrophages, myeloid cells, and monocytes and some neurotoxic substances like glutamate and pyruvic acid, found in elevated level if severe neurotoxicity occurs due to CAR T cell therapy [14].

As we know from the previous researches, the existing clinical symptoms of neurotoxicity are headache, confusion, delirium, language disturbance, seizures, and rarely, acute cerebral edema[55]. The neurological toxicities of the CAR T-cell therapy are often found to be quite similar to Blinatumomab which is a bi-specific antibody that also targets CD19 [16]. Neurological toxicity can even happen in the absence of CRS [56].Sometimes, in the case of neurotoxicity, there is the necessity of mechanical ventilation like intubation to protect the airway and to get rid of respiratory failure.

The other toxicities which have been observed after CAR T cell infusion:

Infusion Related Toxicities:

The infusion process of CAR T cellsshould always be carried out by following the instructions given by the manufacturer. These instructions usually have detailed information about the drug along with the detailed posological information like pre-treatment, pre-medication, monitoring, etc.[14, 57]. According to previous researches the toxicities found are of grade 1-2, so basically they were mildand occurs either during or just after the CAR T cell infusion. The most common toxicity related problems are nausea and vomiting suspected as a result of the dimethyl sulfoxide (DMSO) cryoprotectant and hypotension due to diphenhydramine pre-medication[58].

Tumor Lysis Syndrome:

Tumor Lysis Syndrome or TLS is an oncological emergency that is common in almost every type of cancer. It mainly leads to kidney failure resulting from the accumulation of uric acid derived from nucleic acid breakdown [60]. In contravention with different effective therapeutical techniques like monoclonal antibodies, tyrosine kinase inhibitors, etc. used in case of haematologic malignancies which increase the occurrence of tumor lysis syndrome [59], TLS is merely common even in high-risk situations after CAR T cell infusion [14,57]. Signs and symptoms of TLS should always be monitored. If undiagnosed or diagnosed late, it has reported 20-50% cases leading to death [61, 62].

Graft Versus Host Defense:

ACT with autologous/patient-derived tumor-specific CAR T cells has demonstrated clinical benefit for patients with cancer[7]. Some patients may receive previously some allogeneic stem cell transplantation like bone marrow transplantation, for those cases T cells can be taken from donor origin [14].

Cytopenia:

In this condition, the reduction inthe number of mature blood cells can be observed. This is considered a very common adverse effect and even after the therapy, it can stay for several weeks. There are some significant factors behindcytopenias, it includes the genre like syndrome due to activation of macrophages, cytokine release syndrome in CRS, and mostly the exposure to previous chemotherapeutic procedures [14, 64]. Persistent cytopenias after T-cell therapies or PCTT have shown a very high number of reporting i.e. around 38% with axicabtageneciloleucel[63].Grade 3-4 anemias, thrombocytopenia, leukopenia, neutropenia, and lymphopenia are also reported very often [16].

The prospect of CAR Therapy:

CAR T-cell dependent immunotherapy has come across as a very practical and effective way for the treatment of cancer. The earlier used techniques like Interleukin (IL)-2 and Interferon (IFN)-γ therapy has failed to give a valuable clinical outcome in the early 2000s. After that, Chimeric Antigen Receptor – engineered T-cells came out as state-of-the-art technology, with reported advancement from various disciplines [29]. At the same time, it has to go through multiple challenges for being a highly personalized and living therapeutic system.

The concept of CAR T-cell came across in the late 1980s [30]. After that many changes have been done by various researchers to increase its effectiveness. The first generation of CAR T-cells had certain limitations like very limited persistence and*in-vivo* anti-tumor activity [31]. After that many modifications have been done and the first generation is replaced by second-generation CAR T-cells. The 2nd generation has shown its effectiveness in *in-vivo*tumor killing and T-cell persistence[32, 65]. Multiple domains now have been shown to provide enhancement to *in-vivo* therapy of CAR T-cell. It has also confirmed effective against relapsed and/or refractory B-cell acute lymphoblastic leukemia [32]. In the year 2017, CD-19 directed CAR T-cell therapy kymirahandyescarta got US-FDA approval due to its successful therapeutic outcome in relapsed and refractory B-cell acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma patients [29].

Despite being onthe verge of becoming a treatment process for a wide range of cancer conditions, is has still to overcome certain concerns. One of the challenges it is facing now is to develop an efficient technology as well as a cost-effective manufacturing platform. This is very important for this therapeutic technique to successfully cross the clinical trial phases and commercialization [33]. Achieving a certain number of cells of optimum quality at low cost is very challenging for the manufacturing of CAR T-cells. It also has donor-to-donor variability. Also, to maintain GMP compliance the infrastructure of the entire manufacturing facility and its maintenance becomes very costly and passively affecting the cost of the therapy [34].

New sources of T-Cells are also being searched to obtain T-cells with similar effectiveness [35]. Safety and efficacy are considered as a vital factor for any emerging therapeutic technique. In the Third generation of CAR T-cells, Improvements like co-expression and co-stimulatory molecules are already incorporated to serve the purpose [36,39]. Disease relapse is also a part where this therapy still needs improvement as the relapsed disease is hard to treat and even re-infusion doesn't work in these cases. Although, monitoring for antigen loss and CAR T cell persistence is being performed these days for prediction and prevention [37]. In a review article, it is already reported that CD19 directed CAR T-cell therapy has resulted in an approximately 50% to 60% relapse-free

survival on the 1st year basis in multiple clinical trials which are performed by various institutions [40].

Combination therapies are also under research to have a greater outcome. This combination therapy includes rational use of a certain drug with the therapy to obtain a better result [38]. But it needs a thorough understanding of the symptoms and awaits further research work.

Apart from the cancer therapy researchers are also looking forward to an application of this therapy for Human immunodeficiency virus-1 or HIV-1. Currently, this sector is under research with a hope for future availability [39].

Conclusion:

Chimeric antigen receptor T cell has become an auspicious side of therapy for the future. As we discussed, it has already proved effective for targeting CD19 for beta-cell malignancy, haematological malignancies, and in the management of solid tumors. Despite all this, it still needs to be improved further to increase its effectiveness and reduce all the risk factors it possesses.

It is still under research and hopefully, within a few years it will overcome its drawbacks and it will be designed to be more effective. It is evident by numerous studies that the management of toxicity related problems are not that much stressful. Many companies and research labs are coming forward for manufacturing and research on it. They are looking forward to increasing the availability of this therapy to more people by reducing the cost of the therapy and discover its multidisciplinary uses.

With all this, it can be concluded that currently, it is the most promising therapy for the future. Already it has got many successes in different countries across the world and the amount of research going on in this field will surely make it a very successful treatment for cancer.

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