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New Insights in Role of Cart-T Cell Therapy in Hematological Malignancy: A Systematic Review

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ABSTRACT

Background: The Chimeric antigen receptor T cell (CAR-T cell) is a kind of effector T cell that detects and kills cancer cells without the need for major histocompatibility complex components. The entire process of creating CAR-T cells is not well known. Acute lymphoblastic leukemia, chronic lymphocytic leukaemia, lymphoma, and multiple myeloma are among the haematological cancers for which the CAR-T cell has been employed.

Objectives: Chimeric antigen receptor T cell (CAR-T cell) therapy is a novel adoptive immunotherapy where T lymphocytes are engineered with synthetic receptors known as chimeric antigen receptors (CAR).

Data Sources: Electronic articles and Journal articles about role of Cart-T Cell therapy in hematological malignancy.

Study Selection: This essay was containing data from many resources such as Google scholar, Elsevier, PMC, PubMed, England Journal, and Blood Journal to facilitate achieving the aim.

Data Extraction: If the studies did not fulfil the inclusion criteria, they were excluded. Study quality assessment included ethical approval was gained, eligibility criteria specified, adequate information and defined assessment measures.

Recent Findings: Fourth-generation CARs include the combination of second-generation CARs with an additional element, such as the tumor-killing cytokine IL-12. This type of CAR has improved tumor eradication by releasing cytokines into the tumor microenvironment and recruiting immune cells without prior conditioning. In addition, it has been used to treat virus infections, metabolic disorders and autoimmune diseases in addition to cancers.

Conclusion: CAR T cell therapy has brought a new hope for the treatment of malignant hematological diseases such as acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL) and multiple myeloma (MM).

Keywords: CART-T cell therapy, Clinical applications, Hematological malignancy.

INTRODUCTION

T lymphocyte cells (T cells) are important components of the cell-mediated immune system. These cells are responsible for monitoring and destroying tumour cells or cells that have the potential to become cancerous. Many treatments that cultivate, redirect, and/or boost T lymphocytes towards malignancies have been developed in recent years. T cell-based adoptive immunotherapy is one of them that is discovering novel ways to treat tumours, particularly hematologic tumours. Tissue-infiltrating lymphocytes, TCR-modified T cells, and chimeric antigen receptor T cells (CAR-T cells) are three forms of this new treatment [(1)].

In comparison to CAR-T treatment, the first two procedures do not create a significant alteration of the T cell per se, and hence the effectiveness is not significant. Their advancement is further hampered by the manufacturing process, low success rates, and reliance on immunization. CAR-T cell therapy has been around for over 25 years as a potential treatment regimen. CAR, which has two domains: an extracellular and an intracellular domain, replaces the TCR. The extracellular domain is usually a single-chain fragment (scFv) of an antibody directed toward a cell surface antigen, while the intracellular domain includes fused signaling domains from a natural TCR complex and costimulatory molecules [(2)].

CAR-T cell generations are represented by different intracellular regions. In first generation CARs (lack of costimulatory signal), the signaling endo-domains of costimulatory molecules like CD28, CD134 (OX40), or CD137 (4-1BB) are fused with CD3z. In the second and third generation CARs, the signaling endo-domains of costimulatory molecules like CD28, CD134 (OX40), or CD137 (4-1BB) are fused with CD3z (Fig. 1). When TCR joins with antigen-presenting cells to complete the activation process, this structure mimics the costimulation signal [(3, 4)].

All of these factors combine to make CAR-T cells specialized for a certain type of cancer cell, allowing them to be eradicated. Because a monoclonal antibody against a tumour antigen provides novel T cell specificity for certain types of cancer cells while bypassing the established antigen-presenting process, one of the method's key advantages is that it is not dependent on the major histocompatibility complex for recognition [(5, 6)].

However, a new generation of CARs has piqued scientists' interest. This so-called "fourth generation of CARs" is additionally equipped with a "nuclear factor of activated T cell responsive expression" element for an inducible transgenic product like IL-12 or another cytokine in addition to costimulatory signal(s) like CD28 and (or) CD137 (Fig. 1).

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The specific recognition of a carcinogenic target by CAR-CD3 signaling stimulates the nuclear factor of activated T cell minimal promoter so IL-12 production and release results. To avoid interaction between the promoter of CAR and inducible box, the two trans-gene are separated into different genomic sites [7]. The newest version is being tested in solid tumors, but current records of clinical trials are in sufficient. The whole procedure of CAR-T cell production is complicated (Fig. 2) [8].

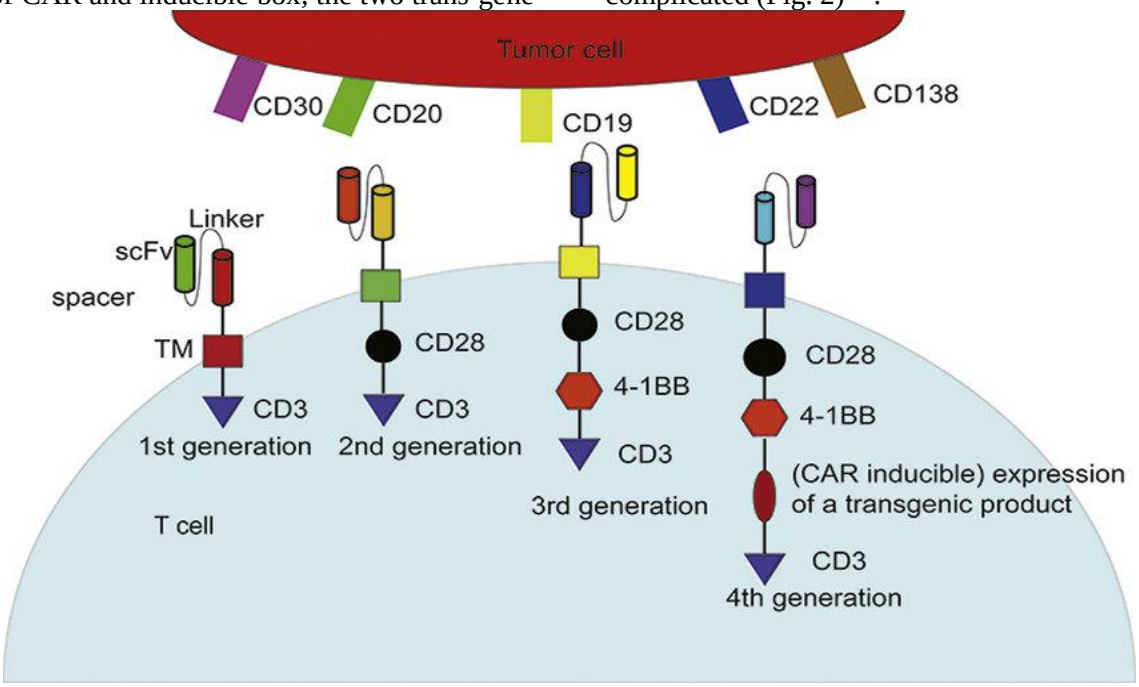

Figure (1): Illustration of basic structure of 4 generations of chimeric antigen receptor T cells (CAR-T cell) and common targets on tumor cells. The whole structure of CARs consisted of anantibody single-chain fragment (scFv, extracellular segment) specifically against a cell surface antigen as well as one or several fused signaling domain(s) from natural TCR complex and costimulatory molecules (intracellular segment). Different intracellular segments represent various CAR-T cell generations. scFv, single-chain fragment. TM, transmembrane region [7].

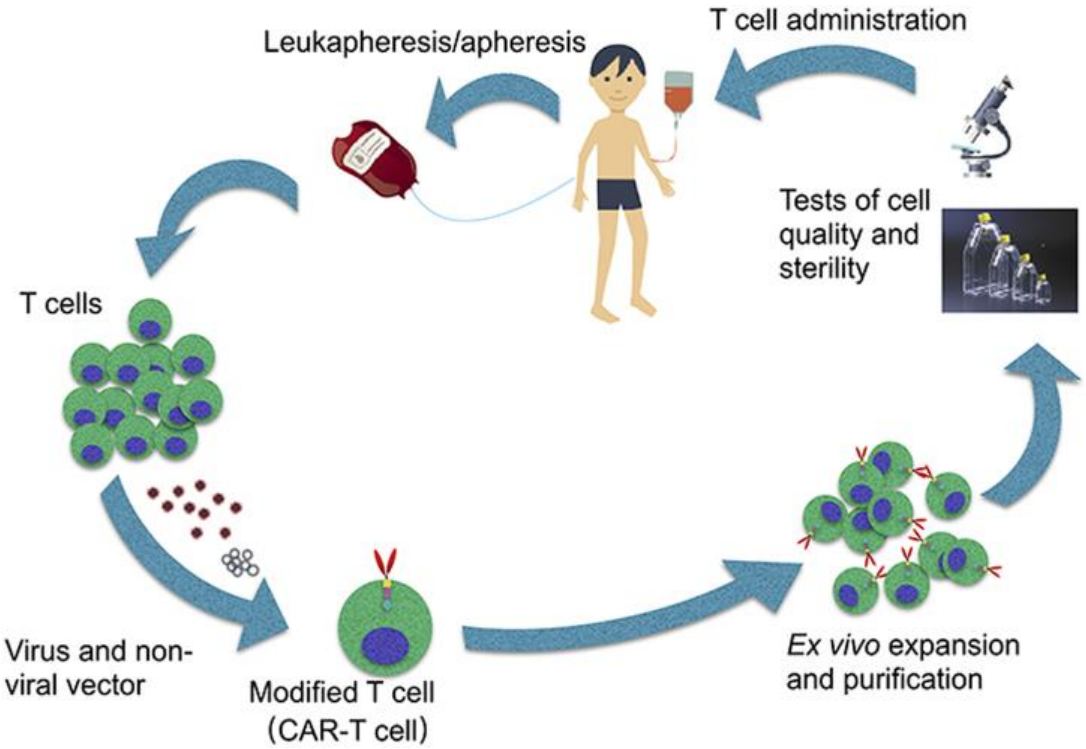

Figure (2): Flow chart of the whole procedure of chimeric antigen receptor T cell (CAR-T cell) production. Firstly, T cells from peripheral blood are collected via leukapheresis, followed by apheresis. Then the T cells are transduced by viral (retroviral or lentiviral) or nonviral vector loading genes of CAR inserted artificially. Next step, the cultured T cells are expanded and purified. Ultimately, cell quality and sterility will be examined before the cell products are infused into patients[8].

Firstly, T cells from peripheral blood are collected by phlebotomy or leukapheresis, followed by apheresis without addition of granulocyte colony stimulating-factor. The reason why granulocyte colony stimulating-factor is excluded is that it may disrupt T-cell proliferation and responsiveness [(9)]. The separated T cells then are transfected with a CAR viral (retroviral or lentiviral) or nonviral vector, where a section of genome DNA is inserted artificially [(9)]. T-cell ex vivo expansion and purification is the subsequent and key step, determining the efficacy of this novel adoptive immunotherapy. The ideal dose is 1 to 5 × 10^8 cells, which, however, is not equal to the CAR-T cell count in human bodies. Finally, tests of cell quality and sterility are necessary, which take 2–4 weeks to complete [(9)]. Before the transduced T cells are administered, a conditioning treatment, including lymphodepleting should be done 2 days ahead for a greater T cell expansion [(9)].

This kind of immunotherapy is commonly used in hematological malignancies such as ALL, CLL, lymphoma, and MM. The most common target is CD19 and the total response is optimistic for ALL [(10)]. Other aims, such as CD20, CD30, and CD138, are also showing some promise. Solid tumours, such as melanoma, sarcoma, and breast cancer, are becoming a new battleground for CAR-T cell therapy. In contrast to hematologic malignancies, most treatments for solid tumours fail due to a lack of and unusual molecular targets for CAR-T cells to assault and manage the tumour microenvironment. Despite a number of concerns concerning safety and efficacy, this approach is undeniably a valuable tool for future cancer immunotherapy. Here, we provide a framework mainly for understanding the applications of CAR-T cells in different hematological cancers, and discuss future directions that will undoubtedly inform the improvement of the effectiveness of these adoptive cell therapies [(11, 12)].

CAR-T Cells for Hematological Malignancies:

1. Acute Lymphoblastic Leukemia (ALL):

ALL is a kind of blood cancer produced by aberrant bone marrow blasts and naive cells that proliferate too much. CAR-T cells are used to treat ALL, particularly relapsed/refractory (r/r) B-ALL, which is fatal [(13)]. CD19 is an activated transmembrane glycoprotein regulating B cells in an antigen receptor-dependent manner, which is expressed throughout the differentiation process of B cells, especially during the malignant transformation of B cells [(14)]. Based on this, CD19 as an ideal target for the treatment of lymphomas is attractive to researchers. **Maude *et al.*** [(15)] used tisagenlecleucel (formerly CTL019) to treat patients with r/r B cell ALL. 75 patients were injected with tisagenlecleucel, and the complete remission rate (CRR) within 3 months achieved 81%. All patients who responded to the treatment were evaluated by flow cytometry, and the minimal residual disease (MRD) was negative. The duration of tisagenlecleucel in the blood was observed for up to 20 months. However, because leukemia cells exhibit the same antigen as normal T cells, the identification of targets for ALL cells poses challenges. Especially, CAR-T cell therapy for ALL always presents cytokine release syndrome (CRS) [(16)].

2. Chronic Lymphocytic Leukemia (CLL):

The most frequent kind of adult leukaemia is CLL, and individuals with multiple r/r CLL have a dismal prognosis. Targeting CD19 with CAR-T cells is an effective way to treat CLL. The CAR-T cell was created by a team of researchers at the University of Pennsylvania to bind to CD3zeta (a signal-transduction component of the T cell antigen receptor) and CD137 (a costimulatory receptor in T cells). After injecting CLL patients with low-dose of autologous CAR-T cells (approximately cells per kilogram of body weight), researchers discovered that the quantity of CAR-T cells increased 1,000-fold over the original input, and the tumour was entirely alleviated. In addition, the CAR was expressed continuously in the blood and bone marrow for 6 months [(17)].

Gauthier *et al.* [(18)] reported 19 cases of r/r CLL patients treated with CAR-T cells and ibrutinib, discovering that the 4-week CRR was 83% and 61% of patients attained MRD by IgH sequencing negative bone marrow response. In the cases with or without ibrutinib, the 1-year PFS after CAR-T cell therapy was 38% and 50%, respectively. The simultaneous application of ibrutinib and CAR-T cell therapy was well tolerated. These studies indicate that CAR-T cells are effective in the treatment of CLL.

3. Non-Hodgkin's Lymphoma (NHL):

NHL is also one of the most common B cell lymphomas. Recently, although chemotherapy, radiotherapy, and hematopoietic stem cell transplantation have gained significant progress in the treatment of NHL, the mortality has not declined. For patients who are resistant to standard treatment regimens, new treatment approaches are imperative. Recently, CAR-T cell therapy has received widespread attention due to its remarkable success in r/r lymphoma [(13)]. **Neelapu *et al.*** [(19)] treated refractory and aggressive B cell NHL patients with KTE-C19 consisting of a single-chain antibody called FMC-63 in the extracellular region, which recognize CD19 on the surface of tumor cells. After treatment, it was found that 62 patients have a total effective rate of 79% and a complete effective rate of 52%. **Chen *et al.*** [(20)] reported a case of r/r acute B cell lymphoblastic lymphoma (B-LBL) with Li-Fraumeni syndrome (LFS), receiving anti-CD19 and anti-CD22 CAR-T cell "cocktail" treatment. The morphology and multiparameter flow cytometry showed that the tumor

was completely relieved, and the MRD was negative. It was worth noting that Burkitt lymphoma (BL) was also one of the most common subtypes of NHL in children, and 5%-10% of patients with a poor prognosis still relapsed after intensive chemotherapy. **Du and Zhang** [21] treated an eight-year-old boy with CAR-T cells targeted to the antigens CD19, CD22, and CD20 sequentially. The results showed that the child had no obvious response to anti-CD19 CAR-T cell therapy and showed progressive disease (PD). After CAR-T cell therapy guided by CD22, the child experienced PR but unfortunately relapsed quickly. Finally, after receiving anti-CD20 CAR-T cell therapy, the child achieved CR. In addition, CD23 and orphan tyrosine kinase receptor (ROR1) have also become potential targets for the treatment of B cell lymphomas, and CAR-T cell therapy has shown great promise in the advancement of the r/r NHL therapy [13].

4. Hodgkin's Lymphoma (HL):

HL is a hematological malignancy originating from B cells and overexpresses CD30, which is a potential therapeutic target [22]. According to a Phase I study, 7 patients with r/r HL were treated with anti-CD30 CAR-T cells, 1 case achieved CR for more than 2.5 years, 1 case sustained CR for almost 2 years, and 3 cases had transient stable disease (SD). It was a remarkable fact that the anti-CD30 CAR-T cell therapy had no toxicity in this study [23]. Furthermore, **Wang *et al.*** [24] performed anti-CD30 CAR-T cell therapy on 11 patients with r/r HL, infusing CAR-T cells per kg of weight. It was indicated that 9 cases (82%) responded to treatment, 1 case (9%) maintained continuous CR, 1 case (46%) achieved PR, and 3 cases (27%) were stable. Tolerable infusion-related fever syndrome occurred in all patients. One patient (9%) had self-limited arthralgia, myalgia, and swelling of both knees for 5 days after 2 weeks of infusion. These results confirm that CD30 has great potential in the treatment of HL.

5. Multiple Myeloma (MM):

MM is a refractory malignancy of bone marrow origin, which is caused by a malignant mutation of plasma cells forming in the final stage of B cell development. CD19 is hardly expressed on the surface of MM cells, and the killing effect of anti-CD19 CAR-T cells on MM cells is weak, which even damages some healthy tissues [25]. Therefore, searching for specific targets expressed on MM cells but not on healthy tissue cells is a potentially effective method for the treatment of MM. **Hosen *et al.*** [26] found a specific therapeutic target (active conformation of integrin) for the treatment of MM. By screening more than 10,000 anti-MM monoclonal antibodies, they identified MMG49 as the MM monoclonal antibody recognizing the integrin $\beta 7$ molecule specifically. It was therefore evident that the transduced MMG49-derived CAR-T cells played an anti-MM role without damaging normal hematopoietic cells. Furthermore, B cell maturation antigen (BCMA, CD269) is another identified target molecule for the treatment of MM. **Xu *et al.*** [27] reported that a female patient with r/r MM after infusion of anti-BCMA CAR-T cells achieved CR. However, patients with a disease-free survival of 7.6 months developed grade 1 CRS, which was mainly manifested as fever and nausea and eventually led to the relapse of MM. Similarly, CD138 (also known as syndecan 1) is highly expressed on the surface of both normal and malignant plasma cells, which has been identified as an attractive target for a long time. **Sun *et al.*** [28] found that T cells from healthy donors and patients with MM could eliminate MM cell lines and primary myeloma cells *in vitro* and *in vivo* when transduced with CD138-specific chimeric antigen receptors. Through preclinical analysis, no off-target tumor cytotoxicity occurred in normal epithelial or endothelial cells. Further, they used SLAMF7 as the target to prepare CAR from anti-SLAMF7 antibody huLuc63 (elotuzumab), indicating that these CAR-T cells had a rapid lysis effect against MM cell lines and primary MM cells *in vitro* [29]. Overall, CAR-T cell therapy for MM has become a promising strategy.

6. Acute Myeloid Leukemia (AMM):

AML is a haematological cancer that affects both adults and children and has a high recurrence rate. In this context, some researchers has revealed that using CAR-T cells to treat AML has had considerable results. A research team [30] demonstrated an anti-CD123 CAR-T cell therapy for the treatment of AML. In addition, **John *et al.*** [31] demonstrated that leukocyte immuno-globulin-like receptor-B4 (LILRB4) was highly expressed on the surface of AML cells. They constructed anti-LILRB4 CAR-T cells successfully, which had a specific recognition effect on AML cells. Although the above CAR-T cell therapy targets for AML have not been used in clinical trials, they provide hope for the further development of treatment for AML.

Disadvantages of CAR Treatment:

1. Cytokine Release Syndrome (CRS):

CRS is a kind of systemic immune stress inflammation produced by the fast proliferation and release of cytokines that occurs when CAR-T cells are implanted into a patient. It is one of the most prevalent side effects of CAR-T cell treatment. Hypotension, fever, neurological abnormalities, and hypoxia are all common symptoms [32].

2. Neurotoxicity:

The second most serious side effect of CAR-T cell treatment is neurotoxicity. Mild headache, verbal problems, visual hallucinations, seizures, severe encephalopathy, and even death are common symptoms of neurotoxicity [33].

3. On-Target/off-Tumor Toxicity:

Biomolecular indicators of haematological malignancies are found in certain normal tissues, particularly lymphoid tissues, in addition to malignant tissues. Despite the relative selectivity of CAR-T cells, on-target/off-tumor toxicity is a term used to describe the degree of tissue damage caused by each approach [(34)].

4. Relapse with CAR-T Cell Therapy:

Although the majority of patients who get CAR-T cell treatment obtain a high level of CR, recurrence of haematological malignancies is possible. The loss of antigen after CAR-T cell treatment (known as target-negative relapse) is one reason of recurrence [(35)].

5. Future Direction:

CAR-T cells have made significant progress in the treatment of haematological malignancies in recent decades, but there are still numerous obstacles to overcome. The key issues are how to increase the efficiency and longevity of CAR-T cells in patients, as well as how to reduce adverse effects following therapy. A new bispecific CAR molecule targets two tumor-specific markers, resulting in improved treatment effectiveness [(34)].

CONCLUSIONS

CAR T cell therapy has given patients with malignant haematological illnesses such ALL, CLL, AML, NHL, HL, and MM fresh hope. However, issues such as CRS, on-target-off-tumor effects, and neurotoxicity must be addressed, as well as the ideal cell dose, enhancement of specificity and effectiveness, resistance to this technique, relapses after a transitory period of CR, and treatment before or after CAR T cell therapy. The difficulties to be resolved are substantial given the complexity and novelty of this therapy.

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