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Chimeric antigen receptor (CAR) T cell therapy in hepatocellular carcinoma; a review of recent advances

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ABSTRACT

Novel therapeutic options such as adoptive immunotherapy have been progressed drastically for treating hepatocellular carcinoma (HCC). Chimeric antigen receptor T cell (CAR-T) therapy is a kind of adoptive immunotherapy that has been associated with promising results in hematopoietic malignancies. However, its application is associated with some obstacles in solid tumors, including heterogeneity of tumor antigens, immunosuppressive microenvironment, and serious adverse complications. In recent years, some progress has been made in this regard, and several preclinical and phase I clinical trial studies have been conducted concerning the application of CAR T-cells in solid tumors. This study will review the possibilities of CAR T cell therapy in HCC, the most common primary liver cancer associated with high morbidities and mortality globally.

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Abbreviations

HCC, Hepatocellular carcinoma; CAR-T therapy, Chimeric antigen receptor T cell Therapy; ACT, Adoptive cell therapy; TIL, Tumor-infiltrating lymphocytes; TCR, T cell receptor; IL-2, Interleukin-2; MHC, Major histocompatibility complex; ECM, Extracellular matrix; EGFR, Epidermal growth factor receptor; MSLN, Mesothelin; PSMA, Prostate-specific membrane antigen; TRUCKS, T cell redirected for universal cytokine-mediated killing; BCMA, B-cell maturation antigen; CEA, Cancer embryogenic antigen; ERBB-2, Erb-B2 Receptor Tyrosine Kinase 2; CRS, Cytokine release syndrome; ICANS, Immune effector cell-associated neurotoxicity syndrome; CAIX, Carboxy-anhydrase-IX; TAG72, Tumor-associated glycoprotein 72; NKG2D, Natural killer group 2 member D; AFP, Alpha-fetoprotein; GPC-3, Glypican-3; MUC-1, Mucin-1; EpCAM, Epithelial cell adhesion molecule; HGF, Hepatocyte growth factor; NKG2DL, Natural-killer group 2 member D ligands;

Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer in adults, and assumes as the fourth leading cause of mortality among cancers globally (1). The incidence of is 9.5 per 100,000 population and its incidence is extremely higher in patients with liver cirrhosis (2). The global trend of HCC is increasing in North America, Europe, and Australia while its trend is almost stable in Asia (3). In addition, HCC is associated with one-year, three-year and five-year global survival rates of, 35%, 19%, and 18% respectively (4), and the survival rate in Asia (34.8%) (4) is relatively lower than Europe (61%) (5).

There are several treating options for HCC, including curative surgical resection, orthotopic liver transplantation, and chemotherapies (6). However, these therapies may be associated with high costs, and some of them such as liver transplantation may not available for everyone; thus, novel therapies such as cellular therapy, nanomedicine-based therapies, and immunotherapy have been attracted vast of attention during recent years. In the current review, we will discuss about a type of immunotherapy, adoptive cell therapy and we will review the application of chimeric antigen receptor (CAR) T-cells, as a novel option for HCC.

Adoptive cell therapy

Cancer immunotherapy which has progressed during recent years, is associated with advantages, including specific and strong immune response to cancerous cells, distant metastasis eradication, and memorial response (7). Adoptive cell therapy (ACT) is a novel approach for cancer immunotherapy, which implies tumor-infiltrating lymphocytes (TIL) infusion, and modifying T cells to display a CAR or specific T cell receptor (TCR) (8). TIL therapy relies on ex vivo expansion of a specific T-cell and its infusion alongside interleukin-2 (IL-2) support (9). TCR-based cancer immunotherapy uses natural or minimally effected TCR, while CAR T-cell therapy implies on artificial receptor presentation to T cells (10). In fact, TCR therapies need cellular presenting components such as major histocompatibility complex (MHC) whereas CAR T-cell therapy, in contrast to TCR therapies, can identify cancerous antigens, independently of MHCs (11).

Recent advances in ACT make this option accessible for numerous patients; however, these therapies majorly target hematologic malignancies, and little is known about the effect of adoptive cell therapy on solid tumor cancers (12). In fact, due to antigen heterogeneity, antigen escape, lack of cytokine and chemokine for T-cell infiltration at the tumor site, and immunosuppressive nature of tumor environment cause challenges for ACT in solid tumors (13). However, some strategies on CAR T-cells, including specify tumor antigens, targeting intracellular neoantigens, engineered CAR T-cells for extracellular matrix (ECM) degradation result in higher infiltration to tumor site, engineered CAR T-cells for prevention of immune resistance, and prevent T-cell exhaustion can overcome these limitations which is discussed recently (14). Indeed, CAR T-cell therapy has been identified for several specific cancer antigens, including Mucin 16, disialoganglioside (GD)-2, epidermal growth factor receptor (EGFR), Mesothelin (MSLN), and prostate-specific membrane antigen (PSMA) (15).

CAR T-cell structure and function

CAR T-cells structured from 1) an extracellular domain, containing monoclonal antibodies and spacer, 2) a transmembrane domain, containing CD8 or CD28, and 3) an intracellular domain, containing CD3ζ sole (first generation of CAR T-cells), or in combination with other molecules such as CD134, CD28, CD137, and CD27 (second and third generations of CAR T-cells) and T cell redirected for universal cytokine-mediated killing (TRUCKs) which are the fourth generation of CAR T-cells (16). In fact, first-generation of CARs only consist of the CD3ζ, while the second generation includes one additional signaling domain such as CD28, the third generation includes two costimulatory domains (e.g., CD28 and CD137), and the fourth generation secrete a transgenic cytokine through CAR signaling (17). Binding specific antigens to the extracellular fragment of a CAR T-cell is associated with phosphatidylinositol and tyrosine kinase signaling activation, resulting in calcium influx in cancerous cells (18).

CAR T-cells are produced from the patient's isolated T-cells through genetical transduction by viral or nonviral gene incorporation (19). After ex vivo genetic modification, culturing, and characterization associated with the expression of chimeric tumor receptors, they reinfuse to the patient (20). This type of therapy is aimed to induce donor's T cells for destroying tumor cells, associated with promising results in hematologic malignancies (21). To date, two types of CAR T-cell based therapy, named Kymriah and Yescarta, have been approved for treating B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma (22). Some reasons, including targeting proper antigens such as CD19, CD20, and B-cell maturation antigen (BCMA), which are dominant in hematologic malignancies, and easily accessibility without the need of MHC complex make them suitable in this regard (23). However, studies revealed that CAR T-cells are not suitable for solid tumors and may associated with fetal outcomes (24).

CAR T-cells applications in solid tumors

As mentioned above, CAR T-cell application in solid tumors encountered several limitations and do not have as efficacy as hematologic malignancies. One of the dilemmas in this regard relates to the unspecific expression of tumor-specific markers in solid tumor cells, associated with on-target off-tumor toxicity (25). In fact, some solid tumor markers, including cancer embryogenic antigen (CEA), Erb-B2 Receptor Tyrosine Kinase 2 (ERBB-2), EGFR, PSMA, GD-2, and MSLN, are expressed in small quantities in normal human cells (26). Therefore, finding the proper tumor specific antigen for targeting tumor cells is a challenge for CAR T-cell therapy. In addition, the clinical application of CAR T-cells is associated with adverse outcomes such as cytokine release syndrome (CRS), and immune effector cell-associated neurotoxicity syndrome (ICANS) (27). In a CAR T-cell study in 2010 on colon cancer, targeting ERBB-2 antigen of cancerous cells, the patient was died due to cytokine release syndrome and respiratory distress, related to low degree expression of ERBB-2 in lung epithelial cells (28). In another study in 2013, application of CAR T-cell designed against carboxy-anhydrase-IX (CAIX) for renal cell carcinoma, was associated with liver toxicity, due to the presence of CAIX in the cholangiocyte (29). Furthermore, antigen escape of the cancerous cells, resulting non-promising outcomes in solid tumors (30).

Indeed, tumor cells can escape from elimination by CAR T-cells by demonstrating alternative forms of a specific antigen. This issue emerges the need for multispecifity CAR T-cells with the ability to induce anti-inflammatory and anti-tumoral properties (31). Moreover, studies revealed that CAR-T cells failed to maintain their ability in the microenvironment of solid tumors, have more trends to blood stream, and have less permeability for vascular endothelium, which make them unsuitable for solid tumors (32, 33).

Considering several barriers for CAR T-cell therapy in solid tumors, recent advances have been made to overcome these pitfalls. In an animal study in 2018 for CAR T-cell treating of peritoneal ovarian cancer by targeting tumor-associated glycoprotein 72 (TAG72), regional intraperitoneal administration of specified CAR T-cell was associated with the reduction of tumor growth, and increment of overall survival (34). In another study in 2018, CAR T-cells designed with the extracellular domain of heregulin-1β, successfully targeted HER3-overexpressing breast cancer cells and had anti-tumoral effect on SK-BR-3 xenograft tumor models (35). In a study in 2016 on prostate cancer, CAR T-cells against PSMA were infused to patient in accordance with IL-2, associated with high engraftment of these cells to prostate tissue and decreasing the amount of PSA (36). In a study in 2019, bi-specific Trop2/PD-L1 CAR T-cell reduced significantly the tumor growth in xenograft model of gastric cancer (37). For colorectal cancer, targeting natural killer group 2 member D (NKG2D) antigen was associated with tumor growth suppression, tumor size depletion and survival increment in xenograft colorectal cancer of mice (38). However, there are few evidences for the application of CAR T-cells for hepatocellular carcinoma.

Novel treatment options, including molecular targeted therapy, immunotherapy, and CAR T-cell based therapy for HCC have been received vast attention during recent years (39). In this context, CAR T-cell therapy can target several antigens of cancerous hepatic cells. Some possible targets for CAR T-cell therapy are specific antigens which is discussed in this manuscript.

Hepatic targets for HCC CAR T-cell therapy

Alpha-fetoprotein

Alpha-fetoprotein (AFP), a plasma protein responsible for liver development during fetus development, has overexpression in hepatocellular carcinoma (40).

AFP can cause tumor growth and invasion, due to its immune effects on dendritic cell cytokine production and inhibit T cell and NK cell proliferation (41). Thus, targeting this antigen can be promising in HCC CAR T-cell therapy. In a study in 2016, direct and intravenous administration of CAR T-cell designed against AFP, which could bind to AFP158-166 MHC complex and significantly decreased both Hep G2 and AFP158-expressing SK-HEP-1 tumoral cells (42). Currently, phase I clinical trial for assessing the safety of anti-AFP CAR T-cell is conducting (NCT03349255) and it seems that this marker can successfully be targeted for CAR T-cell therapy against HCC.

Glypican-3 (GPC-3)

GPC-3, which is a proteoglycan typically found in the fetal liver cells, is overexpressed in HCC and can be used for the diagnosis or assessing the prognosis of HCC (43). This marker controls the cell division and growth, and expressed in more than 70% of hepatic cancerous cells (44). In addition, this marker is almost specific for HCC and not be found in cirrhotic cells or adult healthy cells (45), but it can be seen in lung cancers, ovarian tumors, nephroblastoma or melanoma (46). This marker can interfere with Wnt pathway and stimulate hepatic cancer cells growth or invasion (47); thus, targeting this marker is at the site of attention for HCC.

The application of CAR T-cell against GPC-3 firstly described by Gao et al. in 2014. They showed that third-generation engineered CAR T-cell against GPC-3 can successfully eliminated hepatic cancerous cells in vitro and in vivo (48). Jiang et al. in 2017 showed similar results, in a patient derived xenograft model of HCC (49). In addition, a study in 2020 showed that split CAR T-cell against GPC-3 is associated with tumor suppression, and lower release of inflammatory cytokines, compared to conventional CAR T-cells (50). Currently, three clinical trials completed the patients recruiting (NCT02723942, NCT02395250, NCT03146234) and five clinical trials are recruiting patients for CAR T-cell therapy against GPC-3 (NCT04121273, NCT02905188, NCT03198546, NCT03980288, NCT03884751).

CD147

CD147 is a transmembrane glycoprotein that can be overexpressed in different cancerous cells and is associated with proliferative, anti-apoptotic, and angiogenesis properties (51).

The expression of CD147 in 80% of liver cancerous cells and is associated with invasive properties (52); therefore, targeting this marker is valuable for Immunotherapy against HCC. In a study by Zhang et al. in 2019, a CAR T-cell for targeting CD147 was introduced based on Tet-On 3G system, that allows inducible gene expression only in the presence of doxycycline, was associated with the inhibition of tumor growth in vitro and in vivo (53). In another study in 2020, logic-gated GPC-3, CD-147 CAR T-cell were able to eliminate hepatic cancerous cells which were positive for GPC-3 and CD 147 simultaneously (54). Currently, transfusion of CD147-targeted CAR-T cells through hepatic artery is conducted in a phase I clinical trial (NCT03993743).

Mucin-1 (MUC-1)

MUC-1, a transmembrane glycoprotein, is usually found in several human cancers such as HCC and is associated with resistance against chemotherapy, tumor migration, and invasive properties of hepatic cancerous cells (55). In a study in 2014, first and third generation of MUC-1 specific CAR T-cells were able to kill MUC-1 overexpressed cells, without damages to normal cells (56). In addition, a phase I/II clinical trial is being conducted on patients with refractory solid tumors, including non-small cell lung cancer, pancreatic carcinoma, and hepatocellular carcinoma by anti MUC-1 CAR T-cells (NCT02587689).

Epithelial cell adhesion molecule (EpCAM)

EpCAM is a surface glycoprotein usually overexpressed in carcinomas with an epithelial origin, such as HCC, and is responsible for not only cell-cell adhesion but also cell growth, proliferation, and migration (57). To date, no studies have been published for the application of anti EpCAM CAR T-cell in HCC; although, its application has been evaluated in some solid tumors such as colon cancer (58) and ovarian cancer (59), associated with promising results. A phase I/II clinical trial is currently conducted to assess the ability of anti EpCAM CAR T-cell in some EpCAM positive tumors, including colon cancer, esophageal carcinoma, pancreatic cancer, prostate cancer, gastric cancer, and HCC (NCT03013712).

c-Met

c-Met is a tyrosine kinase receptor, responsible for cell growth and proliferation by the activation of the MAPK/ PI3K/ STAT3 pathway through hepatocyte growth factor (HGF) (60).

The pre-clinical application of anti c-met CAR T-cell against HCC carcinoma has been studied by Jiang et al. in 2021. They showed that bispecific c-Met/PD-L1 CAR-T cells had antitumor properties in hepatic cancerous cells positive for c-Met and PD-L1 in vitro, and in xenograft models for human hepatocellular carcinoma (in vivo) (61). A phase I clinical trial (NCT03672305) also registered in 2018, assessing the safety of c-Met/PD-L1 CAR-T cells against HCC, that has not been started yet.

Natural-killer group 2 member D ligands (NKG2DL)

NKG2D is a receptor of natural killer cells and T-cells, which stimulates the cytolysis effects of these cells through activation by its ligands (NKG2DL) (62). NKG2DLs are over expressed in some human cancers, such as HCC and not present in normal cells (63, 64); thus, NKG2DL can be targeted by CAR T-cells. In a study by Sun et al. in 2019, NKG2D-based CAR T-cell (NKG2D-BBz CAR-T) was able to eliminate hepatic cancerous cells efficiently in vitro and in vivo (65). In addition, a phase I clinical trial is registered, assessing NKG2D-based CAR T-cells therapy for solid tumors, including medulloblastoma, glioblastoma, and HCC (NCT0427046).

CD133

CD133 is a membrane glycoprotein, and a characterized biomarker for cancerous stem cells that causes tumorigenesis, metastasis, and chemoresistance of cancerous cells (66). The role of this marker in the tumor recurrence, and chemoresistance of HCC has also been described (67); thus, it can be used as a target for CAR T-cell therapy. In a phase I trial in 2018 in regards to the application of anti-CD 133 CAR T-cell on solid tumors, 14 patients with HCC were enrolled. It was demonstrated that majority of patients did not develop detectable lesions and CD133+ cells were eliminated. Also, the administration of anti CD133 CAR T-cell was associated with low toxicity (68). In a phase II clinical trial by Dai et al. in 2020, anti CD133 CAR T-cell was infused in 21 adults with HCC, associated with promising antitumor activity and a manageable safety profile (69).

Conclusion

ACT for HCC is a valuable treatment choice for affected patients in regards to the underlying immune and inflammatory pathogenesis of HCC. CAR T-cell based can successfully target HCC specific markers (Figure 1); however, there are limited evidences in this regard. Presently, several clinical trials are conducting to produce a CAR T-cell product against HCC; although, many of them are still at the recruitment process. It seems that the future of CAR T-cell based therapy in HCC is associated with a bright prospective.

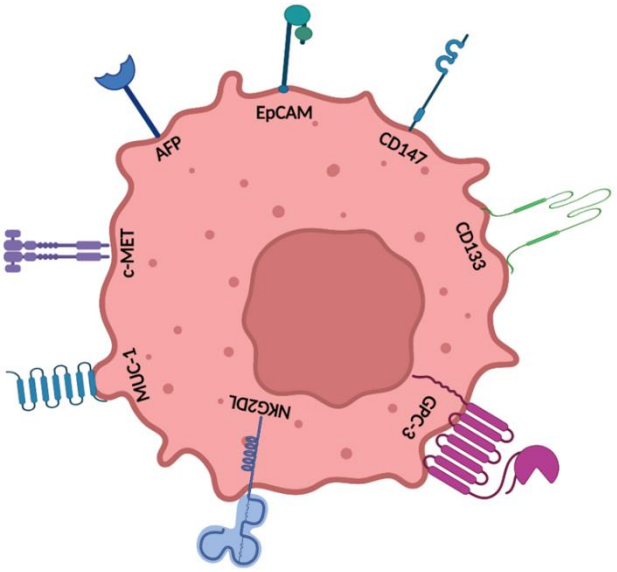

Figure 1. Possible targets for CAR T cell therapy in HCC. CAR T cell therapy: Chimeric antigen receptor T cell Therapy; HCC: Hepatocellular carcinoma.

Declarations

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Conflicts of interest

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Authors' Contributions

M.A.S. conceived and designed the format of the manuscript. K.G. and K.K.T. and H.K.A, drafted and edited the manuscript. M.N. designed the figure. All authors contributed to the critical reading and discussion of the manuscript.

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