Chimeric antigen receptor T cell therapy for solid tumors

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Chimeric Antigen Receptor T Cell Therapy For Solid Tumors

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Abstract

Chimeric antigen receptor T (CAR T) cell therapy has revolutionized the management of lymphoid malignancies. However, it is still in its early phase and is facing many obstacles in solid tumors. Therapeutic challenges in solid tumor lead to tumor target diversification and drive new innovations for the improvement of clinical efficacy. This review showcases early clinical works and sheds light on the most notable successes, drawbacks, and strategies employed to allow CAR T therapy to go full speed ahead.

Keywords: CART for solid tumors, CAR T for solid cancer, Advances in CAR T, Chimeric antigen receptors

1. Introduction

Cellular immunotherapy using chimeric antigen receptor T (CAR T) cells has changed the treatment paradigm for patients with relapsed and refractory hematologic malignancies. CAR T technology introduces a genetically modified receptor into T cells that combines intracellular signaling domains to bypass receptor activation requirements, as well as an extracellular artificial antibody or native protein binding domain to engage the target proteins. It is designed to convey major histocompatibility complex—indeed target recognition for T cells and trigger the killing of target cells. CD19-targeted CAR T cells are effective, produce durable antitumor activity in CD19+ B-cell malignancies, and have remarkable clinical responses, thus leading to the FDA approval of tisagenlecleucel [1,5], axicabtagene ciloleucel [2,3], lisocabtagene maraleucel [4], and brexucabtagene autoleucel [6-8] for lymphomas and acute lymphoblastic leukemia. B-cell maturation antigen—targeted CAR T cells such as idecabtagene vicleucel [9] and ciltaclabtagene autoleucel [10,11] have also been approved for multiple myeloma. Suboptimum CAR T persistence, tumor heterogeneity, and suppressive tumor microenvironment are some of the barriers to the efficacy of cellular immunotherapy for solid malignancies. Many excellent reviews have covered various aspect of CAR T therapy in solid tumors [12,13]. This review will focus on trials with adult clinical data for selected malignancies and malignancies with interesting targets because over 250 clinical trials for various solid tumors are registered under clinicaltrial.gov.

2. Central nervous system cancer

In a phase I clinical trial, 10 patients with glioblastoma (GBM) received epidermal growth factor receptor (EGFR) variant III—directed CAR T cells [14]. Four of the five patients who were enrolled as the first batch of participants achieved stable disease. Ultimately, seven patients needed neurosurgical intervention post-treatment, and CAR T cells were detectable in resected tissues with decreased EGFR expression in some patients. At the time of reporting, 1 patient remained alive for ≥18 months, and 2
patients had progressive disease but remained alive. The median overall survival for this cohort was approximately 8 months. For the first-in-human interleukin-13 receptor (IL13R) a2-directed CD8 CAR T trial, two of three patients with advanced GBM had transient partial response [15]. After further enriching for central memory T cells and adding 4-BB costimulation and a mutated IgG4-Fc linker [16], a patient with aggressive recurrent GBM received intracavity and then intraventricular interleukin-13 (IL13) BB CAR T and achieved complete remission that was sustained for 7.5 months before recurrence at new sites [16].

Preclinical studies showed that human EGFR 2 (HER2)—specific T cells can target HER2-positive GBM stem cells [17]. In a phase I study, 17 patients with progressive HER2+ GBM received HER2-directed CAR multivirus specific T cells and had detectable CAR T cells in peripheral blood for up to 12 month [18]. Two patients had grade 2 seizures/headache attributable to the treatment. One patient achieved a partial response, seven had stable disease, and eight had progressive disease. Diganglioside 2 (GD2) is a glycosphingolipid that is widely expressed in the nervous system.

Most GD2-directed CAR T trials were conducted on pediatric patients [19,20]. One adult study using GD2-CART carrying the RQR8 suicide gene for patients with refractory/relapsed neuroblastoma reported that one of the nine patients had a transient response and grade 2 cytokine release syndrome (CRS) [21]. Overall existing CAR T trials in GBM appear to be safe, and some clinical responses were observed.

3. Gastrointestinal (GI) cancer

An early study using carcinoembryonic antigen (CEA)—directed TCR T resulted in serum CEA reduction and in the regression of colorectal cancer for a patient [22]. Subsequently, CEA-directed CAR T cells for CEA+ metastatic colorectal adenocarcinoma [23] reported that 7 of 10 patients achieved stable disease, with 2 patients remaining stable for 30 weeks and 2 patients having a partial response [23]. Serum CEA level reduction was seen in most patients [23]. In a first-in-human study evaluating allogeneic natural killer group 2D receptor (NKG2D)—directed CAR T therapy in patients with metastatic colorectal cancer [24,25], 2 of 15 patients achieved partial response, and 9 patients had stable disease.

Liver metastases with ineffective host immune response is a poor prognostic marker in GI adenocarcinoma [26]. Katz et al. explored the hepatic artery infusion (HAI) of CEA-directed CAR T with IL-2 support to optimize efficacy for patients with liver metastasis from GI malignancies [26]. Only one patient achieved a stable disease condition, and five patients died of progressive disease. In the subsequent phase Ib HITM-SIR trial [27], with the addition of selective internal radiation therapy using SIRSphere brachytherapy to intraarterial CEA-directed CAR T cells, liver metastases were reduced in four of six patients. With further improvements in delivery via HAI using PEDD technology [28], a complete response within the liver was sustained for 13 months for a patient with metastatic pancreatic adenocarcinoma. Similarly, Zhang et al. used CAR T to target CEA+ metastatic colorectal cancer [29]. Seven of 10 patients had stable disease, with 2 patients having a sustained response for ≥30 weeks. Two patients had partial response, and one patient had liver metastasis shrinkage.

Severe adverse events are always a concern for HER2-directed CAR T cells in GI malignancy. In an early study, a patient with colon cancer metastasis to the lungs died from acute respiratory distress that developed 15 min after the infusion of 1 × 10^10 third-generation HER2-directed CAR T cells [30]. In a phase I trial, Feng et al. treated 11 patients with advanced biliary tract and pancreatic cancers with HER2-directed CAR T therapy after nab-paclitaxel and cyclophosphamide lymphodepletion [31]. One patient had a partial response lasting for 4.5 months, and five patients had stable disease. No significant CRS or neurotoxicity were detected, but two cases of upper GI hemorrhage suggestive of an off-target effect was found. Overall, HER2-CAR T cells appeared to be safe. In a trial with EGFR-directed CAR T cells for metastatic pancreatic carcinoma, 4 of 14 patients achieved partial response, and 8 had stable disease [32]. In a separate study, 14 patients with cholangiocarcinomas and 5 with gallbladder carcinoma were treated with EGFR-directed CAR T cells [33], 1 patient achieved complete remission, and 10 patients achieved stable disease.

CD133 is a glycoprotein that is highly overexpressed in GI tumors such as hepatocellular carcinoma (HCC) and pancreatic, gastric, and intrahepatic cholangiocarcinomas [34]. In 14 patients with HCC treated with CD133-directed CAR T, 7 and 2 patients were pancreatic and colorectal adenocarcinoma patients, respectively; 3 patients achieved partial remission; and 14 patients had stable disease [35]. In a phase II study, among the 21 evaluable patients with HCC who received CD133-directed CAR T, 1 patient achieved a partial response, 14 patients had stable disease, and 6 patients had progressive disease [36]. Glypican-3 (GPC3) and alpha fetoprotein (AFP) are fetoglycoproteins that are detectable at
very low level after birth but increase in malignancy, such as in HCC [37,38]. In a GPC3-directed CAR T study [37], one patient achieved partial response lasting over one year, three patients maintained stable disease, and two patients had progressive HCC disease. In another GPC3-directed CAR T study [38], two patients with HCC achieved partial response, and patient had sustained stable disease after 44.2 months. Data show that one of six patients with AFP+HCC achieved CR and that two patients had partial response [39]. Additional studies utilizing GPC3 [40,41], AFP/HLA-A2 complex-directed [42] CAR T for HCC, and Claudin 18.2-directed CAR T for advanced gastric and pancreatic adenocarcinoma are currently ongoing [43]. mRNA-based CAR T cells has also been used to treat GI malignancies. Two of six patients with pancreatic ductal adenocarcinoma had stable disease after receiving mesothelin-specific mRNA CAR T therapy [44].

4. Genitourinary cancer

Prostate-specific membrane antigen (PSMA) is a glutamate carboxypeptidase II protein that is highly expressed in prostate cancer [45] and is also at the new frontier of prostate imaging [46]. In a phase I trial using second generation PSMA-directed CAR T cells [47], two out of five patients with castration-resistant prostate cancer achieved partial responses, with minor a response in a third patient. Narayan et al. developed PSMA-directed/TGFβ-insensitive CAR T cells for patients with castration-resistant metastatic prostate cancer [48]. PSA level reduction was seen in 6 out of 10 patients. Interestingly, five of seven treated patients in higher cohorts developed grade ≥2 CRS, and there was dose-dependent CAR T cell expansion and tumor tissue infiltration. In a phase I trial, a patient with seminal vesicle cancer received two versions of mucin 1 (MUC1)—directed CAR T cells intratumorally at two independent metastatic lesions. The tumor site received an improved anti-MUC1 pSM3 version of CAR T and showed tumor necrosis [49], thus suggesting potential activities.

5. Lung cancer

EGFR is expressed in epithelial cells, plays important roles in cell proliferation and differentiation, and is also a tumor marker for lung adenocarcinoma [50]. In a phase I study, 11 patients with advanced nonsmall cell lung cancer (NSCLC) received EGFR-directed CAR T cells, 2 patients achieved partial response, and 5 patients had stable disease [51]. Other potential targets for NSCLC include MUC1 (NCT03525782, NCT04025216), prostate stem cell antigen (PSCA), and CEA (NCT02349724 and NCT04348643). CAR T cells studies targeting PD-L1 and CD80/CD86 (NCT03060343) or PD-L1 alone (NCT03330834) are currently being conducted for recurrent or refractory NSCLC. HER2 plays an important role in the pathogenesis of many cancers [52]. However, a fatal case of CAR T therapy due to respiratory distress for a patient with HER2+ colorectal cancer increases the apprehension for the HER2 target in NSCLC. At least one HER2-directed CAR T trial was terminated (NCT02713984) because of safety considerations. Other CAR T targets such as receptor tyrosine kinase—like orphan receptor 1 (ROR1) (NCT02706392), MUC1 (NCT04489862), EGFR (NCT04153799), and CEA (NCT02349724) are being investigated in early phase studies.

6. Breast cancer

Hepatocyte growth factor receptor or c-Met is a tyrosine kinase expressed in >45% of breast cancer cases [53]. In a phase 0 trial [53], six patients received intratumoral injection c-Met-directed mRNA CAR T for metastatic breast cancer with accessible cutaneous or lymph nodes, and two patients showed tumor necrosis and inflammatory reaction. Many clinical trials are currently in phase I or phases I/II without further information. These include CAR T cells directed at mesothelin (NCT02580747 and NCT02792114), c-Met (NCT01837602), MUC1 (NCT02587689, NCT04025216, and NCT04020575), NKG2D (NCT04107142), and ROR1 (NCT02706392). Multiple target-specific CARs have been developed preclinically, including AXL, CD32A, CSPG4, EGFR, Fra, GD2, ICAM-1, integrinavb3, SSEA-4, TEM8, and TROP2.

7. Connective tissue cancer

In a trial with CAR T targeting relapsed/refractory HER2-positive sarcoma [54], 4 of 19 patients achieved stable disease. In another study [55], 10 patients with refractory metastatic HER2+ sarcoma were treated, 2 patients achieved complete remission, 3 patients had stable disease, and 5 patients had progressive disease. Similarly, among six patients with refractory/metastatic HER2+ sarcoma who received HER2-directed CAR T cells [56], one patient with rhabdomyosarcoma metastatic to the bone marrow had a complete response, two patient
remained with stable disease, and three patient had progressive disease. Thus far, HER2-directed CAR T cells are promising and have manageable toxicity.

8. Skin cancer

Metastatic melanoma is the most aggressive skin cancer with poor prognosis. An early CAR T trial targeting VEGFR2, which is a marker for vascular tumors, showed a disappointing result: 23 of 24 patients had progressive disease, and 5 patients experienced serious adverse events [57]. In the phase I CARPETS trial [58], four patients with metastatic BRAF+ melanoma taking dabrafenib ± trametinib were treated with GD2-directed CAR T with pembrolizumab PD-1 blockade. Encouragingly, all patients achieved partial response. Phase I trials are currently ongoing for GD2-specific CAR T (NCT02482532) and GD2-specific CAR T cells combined with standard kinase inhibitor therapy in metastatic melanoma patients. Several phase I or II trials on CAR T targeting melanoma tumor antigens c-Met, hCD70, gp100, NY-ESO-1, IL13R-alpha2, and B7H3 are also ongoing.

9. Multitumor types

Clinical trials on CAR T cell therapy for multiple solid tumor types or targets with multiple binding partners are increasing, with some trials reporting preliminary clinical outcome data. For example, NKR2 is normally expressed on NK, NK T, and activated CD8 T cells and can bind to eight different ligands. The THINK clinical trial was designed for colorectal carcinoma, epithelial ovarian carcinoma, fallopian tube carcinoma, urothelial carcinoma, tri- colorectal carcinoma, epithelial ovarian carcinoma, fallopian tube carcinoma, and ovarian carcinoma, which all express NKR-2 [59]. In a phase I study that investigated mesothelin-directed CAR T cells in malignant pleural mesothelioma, ovarian carcinoma, and pancreatic ductal adenocarcinoma [60], 11 of 15 patients had stable disease. In another phase I mesothelin-directed CAR T cells study [61], 21 patients with MPD (19 patients had primary malignant pleural mesothelioma, and 13 patients received anti-PD1), 1 patient with lung cancer, and 1 patient with breast cancer were treated. Two patients achieved complete metabolic response on PET scan (60 and 32 weeks at the time of reporting), 5 patients had partial response, and 4 patients had stable disease [61]. In a phase I study on ROR1-specific CAR T cells for patients with TNBC and NSCLC [62], one TNBC patient with significant liver disease patient had stable disease for nearly two months. Cell-surface protein PSCA is upregulated in many solid tumors and is correlated with disease stage [63]. In a first-in-human study, 15 patients with pancreatic, gastric, or prostate cancer received ligand-inducible PSCA-directed CAR T therapy [63]. There was rapid cell expansion in all patients, with eight and three patients having stable disease and progressive disease, respectively. Similar to other trials on CAR T involving solid tumors, the majority of patients showed manageable safety profiles and early evidence of biological activities.

10. Future direction

Although CAR T cells for solid tumors showed limited activity in early phase clinical studies, there are several strategies to improve CAR T cell efficacy. Some of these strategies include the reactivation of dysfunctional CAR T caused by a suppressive tumor microenvironment via vaccination [64], improving immune cell infiltration and CAR T cell survival in the tumor via IL-7 and CCL19 expressions in CAR T cells [65], polarizing the tumor microenvironment to a proinflammatory state conducive for effective antitumor immune responses [66], affinity tuning CAR T to enhance tumor antigen binding [67,68], and expressing an Fc-gamma receptor CAR to facilitate multiple therapeutic antibodies and redirect T cells to virtually any antigen expressing tumor cells [69]. The further development and implementation of these new strategies will undoubtedly improve clinical efficacies.

Conflict of interest

Authors declare no conflict of interest.

References


