

Chimeric antigen receptor (CAR) T and other T cell strategies for pancreas adenocarcinoma

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Abstract: Treatments in metastatic pancreas cancer remain based in cytotoxic chemotherapy, and novel treatment strategies are needed. Building on the emerging role of T cell therapy in hematologic malignancies and our understanding of the underlying biology of pancreas cancer, research is growing in the role of T cell therapy for patients with solid tumors in general and more specifically patients with pancreas cancer. This review will focus on describing the biology of T cell therapy and its current applications in pancreas cancer.

Keywords: Pancreas cancer; immunotherapy; chimeric antigen receptor (CAR) T cells

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Introduction

Pancreas cancer represents the third highest cause of cancer-related death in the United States and will affect an anticipated 53,670 patients (1). The majority of patients with pancreas cancer are diagnosed with metastatic disease, and treatments are based in systemic chemotherapy. With the approval of new chemotherapy regimens, including the 5-fluorouracil-based combination with irinotecan and oxaliplatin (FOLFIRINOX) and the combination of gemcitabine and albumin-bound paclitaxel, several reports note overall survival measuring up to 2 years and greater with systemic therapy alone (2-6). While these benefits are tangible for many patients, the improvements with systemic chemotherapy remain incremental. Immunotherapy has changed the way we treat metastatic disease in many solid tumors, including melanoma and lung cancer, bringing durable responses to many of these patients (7-9). To understand whether immunotherapy has a role in the treatment paradigm of pancreas cancer, many ongoing studies are evaluating the following agents as single agents and in combination: immune checkpoint inhibitors, small molecule inhibitors, stromal modulating agents, and genetically engineered and modified T cells. Genetically modified T cells are changing the way we approach and treat hematologic malignancies, and much research is

ongoing to understand if this technology can be used to treat solid tumors as well. The focus of this review is to describe the underlying biology of T cell therapy and ongoing T cell therapy studies in pancreas cancer.

Adoptive T cell transfer

Adoptive T cell therapy exploits the patient's own immune system. After a patient's own T cells are harvested, the T cell receptor can be modified to recognize a specific tumor antigen, expanded, and then reinfused into a patient, allowing the patient's own T cell to target a specified antigen within the context of the patient's own self major histocompatibility complex (MHC). T cells comprise a critical arm of the immune system to identify and adapt to non-self-antigens and targets. Through identification of non-self-antigens, T cell receptors are activated and then stimulated to proliferate, develop into effector cells, and initiate cytolysis against the target cell (10). T cell receptors are comprised of an alpha and beta heterodimer to recognize non-self-antigen presented by the matched MHC and are further stimulated through the associated CD3 complex composed of the zeta-zeta homodimer and heterodimers of epsilon-gamma and epsilon-delta (10).

This adoptive T cell therapy demonstrated promise in

both preclinical and clinical studies using T cells targeting MUC1, an antigen present on pancreas cancer cells, in an HLA-independent fashion. In one study, MUC1-specific T cells were generated via exposure and stimulation of a patient's harvested T cells with a pancreas cancer cell line expressing MUC1. These MUC1-targeted T cells demonstrated *in vitro* activity against multiple pancreas cancer cell lines (11). In a related study in which 20 patients with unresectable or recurrent pancreas cancer were treated with these MUC1-targeted T cells, five experienced stable disease, and one patient experienced a complete response. Mean survival time was 9.8 months (12).

First generation chimeric antigen receptor T cells

In an effort to avoid the MHC restriction needed for conventional T cell receptor activation, T cells can be transduced with genes encoding a chimeric antigen receptor (CAR), which includes both an extracellular binding domain and an intracellular activation domain often using the CD3 T cell activation domain. This extracellular binding domain includes an antibody recognizing tumor antigens, thus avoiding the MHC restriction needed for conventional T cells and allowing for the engineering of CAR T cells to express receptors specific for many different tumor antigens (10). By transducing both a CAR and a T cell activation domain, these first-generation CAR T cells identify and attack tumor antigens and also expand with the help of T cell activation through the CD3 complex. CAR T cells are then infused back into a patient to stimulate an immune response against the target antigen. Additionally, tumor lysis may result in cytokine production, further stimulating an immune response (13). Although first generation CAR T cells have shown some ability to persist and cause anti-tumor activity, initial studies demonstrate that anti-tumor activity, expansion, and persistence are sub-optimal (14-16). To combat these challenges, first generation CAR T cells have been modified with the addition of co-stimulatory molecules to create so-called second-generation CAR T cells.

Second generation chimeric antigen receptor T cells

Second generation CAR T cells are further modified with the addition of a second co-stimulatory cytoplasmic signaling domain such as 41-BB (also known as CD137), OX40 (also known as CD134), CD28, inducible costimulator (ICOS), and DAP10 (17-28). Stimulation of these costimulatory intracytoplasmic domains with CAR

activation by tumor antigen allows production of IL-2 and other stimulatory cytokines to facilitate activation and expansion of these CAR T cell populations, as demonstrated pre-clinically through increased IL-2 production after antigen binding to a CD28-derived-CD3 zeta CAR compared to decreased IL-2 production with antigen binding to a CAR T cell without CD28 (27,29-31).

Promising responses in CD19 expressing hematologic malignancies

Thus far, CAR T cells have been evaluated most extensively in CD19 expressing B cell malignancies with most promise in B-cell acute lymphoblastic leukemia (B-ALL). The largest experience to date in adults has been reported by Park and colleagues in which 37/45 patients experienced morphologic complete response, and 13/37 were able to undergo an allogeneic hematopoietic stem cell transplant. Six-month overall survival did not differ between patients who did or did not undergo allogeneic hematopoietic stem cell transplant. Most common toxicities in this group included transient B-cell aplasia, cytokine release syndrome (CRS), and neurologic toxicities (32-34). At Fred Hutchinson Cancer Research Center, 24/26 evaluable patients with B-ALL achieved a complete response (35).

CD19-targeted CAR T cells have shown promise in pediatric B-ALL studies as well. Investigators from University of Pennsylvania have demonstrated that 50/53 patients experienced a morphologic complete response (36,37). Investigators from the National Cancer Institute have shown that 14/20 patients with relapsed B-ALL achieved and maintained a complete response as well (38). At Memorial Sloan Kettering Cancer Center, initial results have demonstrated that 2/4 patients with relapsed B-ALL experienced a complete response with treatment with CD19-targeted CAR T cells (39).

Many ongoing studies are evaluating the efficacy of CAR T cells in patients with other CD19 expressing B cell malignancies, including multiple myeloma, non-Hodgkin lymphoma, and chronic lymphocytic leukemia (40). Recently completed studies evaluating CAR T cells in other CD19 B cell malignancies have demonstrated mixed responses (40,41).

Emerging data and experience in solid tumors

Given the promising responses seen with CAR T cells in CD19 expressing hematologic malignancies, efforts are

underway to understand whether this emerging technology can be applied to solid tumors. CAR T cells have been created to target many tumor antigens in various solid tumors including pancreas cancer, mesothelioma, ovarian cancer, renal cell carcinoma, and melanoma (15,42-47). Although few studies with adoptive T cell therapy in pancreas cancer have been completed thus far, ongoing studies for patients with pancreas cancer are evaluating many tumor antigens, such as carcinoembryonic antigen (CEA), mesothelin, and others as described below.

CEA

Routinely used as a serum marker for monitoring patients with gastrointestinal malignancies, CEA is also present on the tumor cell surface of 75% of pancreas cancers (48-50). Preclinical studies have demonstrated that CAR T cells targeting CEA have a cytotoxic effect on a pancreas cancer mouse model (51). Although final results have not yet been published, a CAR T cell study evaluating CEA-targeted CAR T cells was halted early due to respiratory complications, highlighting the risks and caution needed when pursuing these studies (52,53). Several studies are ongoing to better understand the safety and maximum tolerated dose of CAR T cells targeting CEA through both systemic administration (NCT02349724 Southwest Hospital China) and various local means of administration to the liver (NCT02850536 Roger Williams Medical Center, NCT 02959151 Shanghai Cancer Hospital).

Mesothelin

Mesothelin is expressed in many tumors, including 85–90% of mesotheliomas and 80–85% of pancreas cancers (54-57). Mesothelin's utility as a practical target for immune targeting was confirmed in a phase 1 study in which an anti-mesothelin immunotoxin SS1P was administered to patients with mesothelin-expressing tumors (58). Of 33 patients treated, 23 experienced disease control with 4 patients having a minor response and 19 patients having stable disease (58). In pancreas cancer, expression of mesothelin is present primarily in pancreas adenocarcinomas but not in normal tissue (59,60). Mesothelin is associated with tumor invasion (59,60). In preclinical studies, CAR T cells targeting mesothelin demonstrated response in pancreas cancer cell lines (61).

Preliminary results presented by Beatty and colleagues

demonstrated the feasibility of mesothelin-specific CAR T cell therapy for patients with solid tumors, including 1 with metastatic pancreas cancer (62). Follow-up data noted that 2 out of 6 patients experienced stable disease, including 1 with stable disease for greater than 4 months while off cytotoxic chemotherapy (63) (NCT01897415 University of Pennsylvania). Final results are pending.

Many ongoing studies are evaluating the role of mesothelin-targeted CAR T cells in pancreas cancer (NCT01583686 National Cancer Institute, NCT02159716 University of Pennsylvania, NCT02465983 University of Pennsylvania/University of California, San Francisco, NCT03054298 University of Pennsylvania, NCT02930993 China Meitan General Hospital, NCT 02580747 Chinese PLA General Hospital). Novel approaches of locally administered CAR T cells are also being further investigated (NCT02706782, Renji Hospital in China, NCT01897415, NCT02706782, NCT02959151 Shanghai Cancer Hospital). Additional studies are also ongoing evaluating the role of mesothelin-targeted CAR T cells in mesothelioma and in breast cancer with pleural involvement (NCT02414269 Memorial Sloan Kettering Cancer Center, NCT02792114 Memorial Sloan Kettering Cancer Center).

Prostate stem cell antigen

Harnessing the overexpression of prostate stem cell antigen (PSCA) in pancreas cancer, PSCA-targeted CAR T cells demonstrated promise in an *in vivo* mouse model of pancreas cancer, supporting further evaluation of this target (64,65). A novel CAR T cell construct, BPX-601, has been developed with a variable chain fragment targeting PSCA and with an inducible co-stimulatory domain activated by the small molecule rimiducid. The safety of BPX-601 is being evaluated in an ongoing clinical trial (NCT02744287 Bellicum Pharmaceuticals).

Other antigens

CD24

CD24, a marker of cancer stem cells, is also being evaluated as a therapeutic target in pancreas cancer. Given the prevalence of early disseminated metastases and the treatment refractory nature of this disease, cancer stem cells are thought to play a role in the development and proliferation of pancreas cancer (48,66). Preclinical studies have demonstrated that CD24-targeted CAR T cells caused tumor eradication in a

xenograft model of pancreas cancer (67).

MUC1

MUC1 is overexpressed in pancreas cancer, and preclinical studies have demonstrated promising responses *in vivo* studies of MUC1-targeted CAR T cells in mice (68,69). A case report was presented of minimal toxicity and tumor necrosis after intra-tumoral administration of MUC1-targeted CAR T cells in a patient with MUC1-expressing seminal vesicle cancer (70). Studies are ongoing to evaluate the safety and efficacy of MUC1-targeted CAR T cells (NCT02587689 PersonGen BioTherapeutics Co., Ltd., NCT02617134 PersonGen BioTherapeutics Co., Ltd.).

MUC16

MUC16, also known as CA125, is a well-known marker in gynecologic malignancies and is also overexpressed in pancreas cancer cell lines and not expressed in normal pancreas (71). *In vitro* studies have demonstrated antitumor activity and eradication in a mouse model of peritoneal cancer treated with MUC16-targeted CAR T cells targeting MUC16 (72). Studies are ongoing evaluating the safety and maximum tolerated dose of MUC16-targeted CAR T cells in patients with gynecologic cancers (73).

Many studies are ongoing for patients with pancreas cancer evaluating CAR T cells in pancreas cancer against various other targets, including CD133, CD70, epidermal growth factor receptor (EGFR), ERBB2, natural killer receptors, and others (Table 1).

Challenges and opportunities in pancreas cancer

Stromal modulation

Several features of pancreas cancer contribute to the chemoresistance and poor prognosis of pancreas cancer. One such feature is the dense stroma surrounding pancreas cancer, which is thought to limit chemotherapy delivery to the tumor. The stroma itself represents a promising therapeutic target to not only facilitate chemotherapy delivery but also to propagate a more favorable tumor microenvironment, and many studies are ongoing or have been recently completed to evaluate the role of stromal targeting in this population. For instance, a recent study of the combination of chemotherapy and PEGPH20 targeting hyaluronidase demonstrated promising activity, and several studies are ongoing evaluating

this combination (NCT02715804, NCT02487277, NCT02921022) (74,75). Heparanase was also a promising target, although a recently completed study of the heparanase targeted drug M402 with gemcitabine and nab-paclitaxel was recently stopped early due to futility (76). Chemokine receptors, such as CXCR2, have also been a promising target. A recent study of PF04136309, a CXCR2 antagonist, with FOLFIRINOX demonstrated promising results, and CAR T cells co-expressing chemokine receptors are being explored to enhance CAR T cell trafficking to the tumor (77-79). Building on these strategies, several CAR T cell studies are also targeting the tumor stroma. For instance, fibroblast activation protein (FAP) is expressed on stromal cells, and FAP-targeted CAR T cells have been developed and demonstrated tumor activity in mouse models but also off-tumor on-target toxicity, which may limit further evaluation (80).

Immunosuppressive tumor microenvironment

Another challenge in pancreas cancer is the creation of an immunosuppressive tumor microenvironment that allows pancreas cancer to evade the immune system. First, pancreas cancer is thought to harbor an increased number of T regulatory cell populations, partly via increased expression of chemokine receptor type 5 (CCR5). Increased presence of T regulatory cells is thought to contribute to T cell inhibition via increased inhibitory cytokine production such as TGF-beta and IL-10 (48,81,82). Also, upregulation of inhibitory ligands such as programmed death-1 (PD-1) results in T cell inhibition. Single agent use of immune checkpoint inhibitors has resulted in durable and dramatic clinical response in many cancers, including lung cancer, melanoma, renal cell carcinoma, and others. While single agent use of checkpoint blockade has been underwhelming in pancreas cancer thus far, use of checkpoint blockade in combination with CAR T cells may circumvent these issues (83). To augment the response of CAR T cells, combination therapy with immune checkpoint blockade and CAR T cells has demonstrated restored and prolonged efficacy of CAR T cells (84). Consequently, novel combinations of immune checkpoint blockade with mesothelin-targeted CAR T cells (NCT03182803 Shanghai Cell Therapy Research Institute, NCT03030001 Ningbo Cancer Hospital), MUC1 expressing CAR T cells (NCT03179008 Shanghai Cell Therapy Research Institute) are also ongoing.

Table 1 Ongoing or recently completed trials with chimeric antigen receptor T cells in pancreas cancer

Targets	Clinicaltrials.gov identifier	Sponsor	Status
CD133	NCT02541370	Chinese PLA General Hospital	Recruiting
CD70	NCT02830724	National Cancer Institute	Recruiting
CEA	NCT02850536	Roger Williams Medical Center	Recruiting
CEA	NCT02416466	Roger Williams Medical Center	Ongoing but not recruiting
CEA	NCT02349724	Southwest Hospital, China	Recruiting
CEA	NCT01723306	Roger Williams Medical Center	Suspended
CEA	NCT00004178	Roger Williams Medical Center	Completed
CEA	NCT01212887	Cancer Research UK	Terminated due to safety concerns
Claudin 18.2	NCT03159819	Changhai Hospital	Not yet open
EGFR	NCT02873390	Ningbo Cancer Hospital	Recruiting
EGFR	NCT02862028	Shanghai International Medical Center	Recruiting
EGFR	NCT03182816	Shanghai Cell Therapy Research Institute	Recruiting
EGFR	NCT01869166	Chinese PLA General Hospital	Recruiting
EpCAM	NCT03013712	First Affiliated Hospital of Chengdu Medical College	Recruiting
GD2	NCT02992210	Shenzhen Geno-Immune Medical Institute	Recruiting
Glypican-3	NCT02932956	Baylor College of Medicine	Not yet open
HER2	NCT02713984	Zhi Yang	Recruiting
HER2	NCT00924287	National Cancer Institute (NCI)	Terminated due to patient death on study
HER2	NCT00889954	Baylor College of Medicine	Ongoing but not recruiting
Mesothelin	NCT03182803	Shanghai Cell Therapy Research Institute	Recruiting
Mesothelin	NCT03054298	University of Pennsylvania	Recruiting
Mesothelin	NCT03030001	Ningbo Cancer Hospital	Recruiting
Mesothelin	NCT02959151	Shanghai GeneChem Co., Ltd.	Recruiting
Mesothelin	NCT02930993	China Meitan General Hospital	Recruiting
Mesothelin	NCT02706782	Shanghai GeneChem Co., Ltd.	Recruiting
Mesothelin	NCT02580747	Chinese PLA General Hospital	Recruiting
Mesothelin	NCT02159716	University of Pennsylvania	Completed
Mesothelin	NCT01897415	University of Pennsylvania	Ongoing but not recruiting
Mesothelin	NCT01583686	National Cancer Institute (NCI)	Recruiting
Mesothelioma	NCT02465983	University of Pennsylvania	Ongoing but not recruiting
MG7	NCT02862704	Xijing Hospital	Recruiting
MUC1	NCT03179007	Shanghai Cell Therapy Research Institute	Recruiting
MUC1	NCT02587689	PersonGen BioTherapeutics (Suzhou) Co., Ltd.	Recruiting
Natural killer receptor	NCT03018405	Celyad	Recruiting
PSCA	NCT03198052	Second Affiliated Hospital of Guangzhou Medical University	Not yet open
PSCA	NCT02744287	Bellicum Pharmaceuticals	Recruiting

CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; PSCA, prostate stem cell antigen; EpCAM, epithelial cell adhesion molecule.

Another approach has been to further modify CAR T cells to thrive in an immunosuppressive environment. Mohammed and colleagues evaluated the role of the immunosuppressive cytokine IL-4. They created a molecule combining the IL-4 receptor to the endodomain of the immune-activating IL-7 receptor. Transduction of this molecule into a PSCA-targeted CAR T cell allowed the CAR T cell to persist and thrive in an IL-4 rich microenvironment using an IL-4 producing prostate stem cell antigen (PSCA)-expressing tumor cell line (85).

Similarly, use of other immune modulatory agents such as tumor necrosis factor alpha-receptor antibodies and diabetes medication such as metformin and rosiglitazone are novel therapeutic approaches and may provide opportunities to be combined with CAR T cell to facilitate improved activity of CAR T cell (86-88).

Safety concerns with chimeric antigen receptor T cells

While CAR T cell therapy has provided much excitement in the hematologic malignancies and promise in solid tumors, several drawbacks and concerning toxicities have also arisen. The biggest challenge in application of CAR T cell technology to solid tumors is that antigens present on the tumor cell surface are nearly always present in some level on normal tissue as well, increasing risk of autoimmune on-target toxicity. Also, there have been several treatment-related deaths on clinical trials using CAR T cells in hematologic malignancies, related to neurologic toxicity and cerebral edema (89). Finally, CRS remains a significant concern and requires monitoring with an experienced team and frequently monitoring in an intensive care unit setting due to the risks of rapid progression and decline (41,90).

Many strategies have been developed to help monitor and treat these side effects, particularly among centers treating a higher volume of these patients. First, transduction of a “suicide” gene into the CAR T cell is often used. For instance, transduction of the epidermal growth factor receptor into the CAR T cell allows for apoptosis with administration of cetuximab, an FDA-approved drug targeting EGFR which can be well-tolerated and with a well-known safety profile. Use of the IL-6 receptor antagonist tocilizumab is also used to help treat CRS. Most important though is a high degree of suspicion for toxicity, early intervention, and appropriate use of reversal mechanisms such as tocilizumab or triggers for the suicide gene used in that CAR T cell construct (41,90).

Future directions

Pancreas cancer remains a disease treated by systemic chemotherapy primarily, and novel treatment strategies are needed. Immunotherapy in the form of checkpoint inhibitors has revolutionized the way we treat lung cancer, melanoma, and several others, and T cell therapy has similarly provided dramatic and frequently durable improvements in a challenging population of patients with refractory CD19+ hematologic malignancies. We remain hopeful that T cell therapies will provide a novel opportunity for patients with pancreas cancer given the multitude of targets and opportunities for both local administration of CAR T cells and combination therapy with other immunotherapies and stromal modulating agents.

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Footnote

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