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Immunotherapy for pancreatic cancer

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Abstract

Pancreatic cancer, a highly lethal cancer, has the lowest 5-year survival rate for several reasons, including its tendency for the late diagnosis, a lack of serologic markers for screening, aggressive local invasion, its early metastatic dissemination, and its resistance to chemotherapy/radiotherapy. Pancreatic cancer evades immunologic elimination by a variety of mechanisms, including induction of an immunosuppressive microenvironment. Cancer-associated fibroblasts interact with inhibitory immune cells, such as tumor-associated macrophages and regulatory T cells, to form an inflammatory shell-like desmoplastic stroma around tumor cells. Immunotherapy has the potential to mobilize the immune system to eliminate cancer cells. Nevertheless, although immunotherapy has shown brilliant results across a wide range of malignancies, only anti-programmed cell death 1 antibodies have been approved for use in patients with pancreatic cancer who test positive for microsatellite instability or mismatch repair deficiency. Some patients treated with immunotherapy who show progression based on conventional response criteria may prove to have a durable response later. Continuation of immune-based treatment beyond disease progression can be chosen if the patient is clinically stable. Immunotherapeutic approaches for pancreatic cancer treatment deserve further exploration, given the plethora of combination trials with other immunotherapeutic agents, targeted therapy, stroma-modulating agents, chemotherapy, and multi-way combination therapies.

Key Words: Pancreatic adenocarcinoma; Pancreatic cancer; Immunotherapy; Immune checkpoint inhibitor

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Core Tip: This review article addressed the role of immune cells in the development of pancreatic cancer, the tumor microenvironment, the cancer immunity cycle, the mechanisms and efficacies of immunotherapeutic drugs in pancreatic cancer, and the response criteria for use in trials aimed at testing immunotherapeutics. The strength of this article includes 2 characteristic tables for basic mechanisms and clinical outcomes related with pancreatic cancer immunotherapy.

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INTRODUCTION

Pancreatic cancer, which most commonly occurs as pancreatic ductal adenocarcinoma (PDAC), is a highly lethal cancer with the lowest reported 5-year survival rate (9% for all stages of the disease) among various cancers^[1]. The dismal prognosis for PDAC is attributable to the tendency for a late diagnosis of this disease, a lack of biomarkers, aggressive local invasion, early metastatic nature, and resistance to systemic therapies^[2,3]. Decades of extensive scientific and clinical research, as well as advances in the diagnostic and therapeutic modalities for PDAC, have resulted in a modest extension of survival among patients with PDAC. Most patients with pancreatic cancer eventually experience disease progression, even after complete surgical resection of their tumors^[4,5]. Projection of cancer incidence and deaths to 2030 indicates that pancreatic cancer will be the second most common cause of cancer-related deaths^[6].

Pancreatic cancer can suppress the host immune response, either directly or *via* immune cells in the tumor microenvironment^[7]. The abundant tumor stromal content of pancreatic cancer is responsible for its high invasiveness and resistance to treatment^[2,8]. In particular, immune cells make up approximately 50% of the cell mass of a PDAC tumor^[2]. Tumor-associated macrophages, myeloid-derived suppressor cells (MDSC), and regulatory T (Treg) cells are the major immune cell types responsible for the immunosuppressive activity of the tumor microenvironment^[2,4].

Activation of negative regulatory pathways, or the so-called "checkpoints," by cancer cells leads to suppression of the cytotoxic T (Tc) cells and allows the cancer to grow undisturbed^[9]. The rigidity of the extracellular matrix (ECM) in the PDAC microenvironment, related with dense fibrosis, further contributes to therapeutic resistance in PDAC by compressing blood vessels. This compression reduces perfusion, thereby lowering the concentration of chemotherapy drugs in the stroma and concomitantly impeding the delivery of the anticancer drugs to the tumor cells^[2,10].

One alternative to chemotherapy drugs as a cancer treatment is to use immunotherapy, the science-driven therapeutic approach of mobilizing the immune system to destroy cancer^[11]. The United States Food and Drug Administration (FDA) has approved several new immunotherapies in the past few years, including: (1) Immunomodulatory antibodies that block checkpoints in patients with a variety of cancers, such as melanoma, non-small cell lung cancer, Hodgkin's disease, solid tumors with high microsatellite instability (MSI-h), etc.; and (2) Chimeric antigen receptor (CAR)-modified T cell immunotherapy for B cell malignancies^[12,13]. Approved immune checkpoint inhibitors include antibodies that block cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed cell death 1 (PD-1), programmed cell death ligand 1 (PD-L1), and combinations. In association with pancreatic cancer immunotherapy, FDA recently approved the use of anti-PD-1 (pembrolizumab and nivolumab) immunotherapy for all solid tumors with MSI-h or mismatch repair deficiency.

This review addresses the role of immune cells in the development of pancreatic cancer, the tumor microenvironment, the cancer immunity cycle, the mechanisms and efficacies of immunotherapeutic drugs in pancreatic cancer, and the response criteria for use in trials aimed at testing immunotherapeutics.

LITERATURE REVIEW STRATEGY

The PubMed database was used to search publications related to immunotherapy for pancreatic cancer employing the following keywords: (“pancreatic cancer”, OR “pancreatic adenocarcinoma”) and (“immunotherapy” OR “vaccine” OR “antibody”). Pertinent articles published in the English language literature were reviewed. All of the references were manually verified, and all reference lists in the retrieved articles were scrutinized to identify any additional articles that might have been missed by the PubMed search.

TUMOR MICROENVIRONMENT AND THE ROLE OF IMMUNE CELLS IN PDAC DEVELOPMENT

The pancreatic tumor microenvironment represents plentiful fibrotic stroma comprising a variety of cells and extracellular matrix components with blood vessels and nerves^[7].

Cancer-associated fibroblasts and tumor microenvironment

Activated pancreatic stellate cells, pan-endothelial cells, and infiltrating immune cells such as MDSC, Treg cells, and tumor-associated macrophages encircle the cancer cells during pancreatic tumorigenesis^[14,15]. Interactions between these cells create the PDAC stroma—suitably termed the tumor microenvironment—that supports the process of carcinogenesis and shields the cancer cells from the anti-tumorigenic immune system^[16], although some components of the tumor stroma can act to restrain tumor growth^[17]. Activated pancreatic stellate cells, the so-called cancer-associated fibroblasts (CAFs), are the predominant source of ECM proteins and collagen that form desmoplastic PDAC stroma^[18]. The PDAC stroma consists of cellular and acellular components, such as CAFs, infiltrating immune cells, blood vessels, and ECM components that include collagen, fibronectin, proteoglycans, hyaluronic acids, and enzymes^[2]. This desmoplastic stroma may act as an inflammatory shell that impairs the responses of cancer cells to chemotherapy and radiation^[19,20].

The CAFs interact with pancreatic cancer cells, endothelial cells, and inflammatory cells, although CAFs are not considered an immune component of PDAC^[18,21]. The PDAC cells first recruit CAFs to their area and promote fibrogenesis. The CAFs reciprocate by promoting cancer cell proliferation and migration^[18,19,22]. Interference with T-cell function by CAF is mediated by immune crosstalk mediated by activation of transforming growth factor beta (TGF- β) and production of C-X-C motif chemokine 12 (CXCL12)^[23]. The *in vitro* co-culture of PDAC cells with pancreatic stellate cells enhances PDAC cell proliferation by way of growth factors and cytokines release^[2]. CAFs also stimulate angiogenesis by endothelial cells through the expression of angiogenic factors, including vascular endothelial growth factor (VEGF), angiopoietin-1, periostin, and hypoxia inducible factor-1^[18].

M2-polarized tumor-associated macrophages

Macrophages normally act as phagocytic cells that destroy damaged cells. However, cancer cells can escape immune surveillance by phagocytic cells through generation of the 'don't eat me' signal by driving CD47 overexpression^[24,25]. In fact, macrophage infiltration is increased in the PDAC microenvironment when compared to normal pancreatic tissue^[21,24]. Tumor-induced cytokines, such as macrophage colony-stimulating factor, chemokines, and vascular endothelial growth factor, recruit circulating blood monocytes into the PDAC microenvironment and induce their differentiation into resident tumor-associated macrophages that have the M2 phenotype^[21].

Two discrete states of 'polarized' activation have been recognized for macrophages. While M1 macrophages are classically activated by T helper 1 cytokines, such as interferon- γ , interleukin-1 β (IL-1 β), and lipopolysaccharide, the M2 macrophages are alternatively activated by T helper 2 cytokines, such as IL-4 and IL-13^[26]. These macrophage subtypes are a functional division, and specific signals induce macrophage polarization from the M1 subtype to the immune-suppressive tumor-associated M2 subtype, and *vice versa*. The M2-polarized tumor-associated macrophages can suppress Tc cells by secreting IL-10 and producing carbon monoxide. Resultantly, the M2 subtype macrophages are an important component of the immune cells in the PDAC microenvironment and are associated with a poor

prognosis in patients with PDAC^[21,24].

MDSC

The MDSC represent a mixture of immature cell types (monocytic or granulocytic) with a potent immune suppressor function^[27-29]. MDSC suppress both innate and adaptive immunity, and they impede T cell activation by diverse mechanisms^[27]. An accumulation of MDSC has been described in patients with PDAC and in experimental animals with pancreatic cancer^[4,21,28]. Cancer-derived signals, such as VEGF and granulocyte-macrophage colony-stimulating factor (GM-CSF), block the maturation of myeloid cells, leading to accumulation of MDSC in the tumor microenvironment, as well as in the blood, lymph nodes, and bone marrow^[21,28,30]. Therefore, pro-inflammatory mediators that can induce gathering of MDSC in the tumor microenvironment represent attractive therapeutic targets in anti-tumor strategies. Elevated levels of MDSC are associated with progression of disease, as well as poor prognosis in patients with PDAC^[21,31].

Regulatory T cells

CD4⁺ Foxp3⁺ Treg cells are accumulated in the PDAC microenvironment from the early pancreatic tumorigenesis stage through invasive cancer^[15,21,32]. PDAC microenvironment has significantly higher number of Treg cells than non-neoplastic inflamed pancreatic stroma has^[15,32]. Treg cells suppress effector T-cell activation, proliferation, and cytokine production for minimizing deleterious immune-mediated inflammation in the normal host. Foxp3 is the transcription factor that specifies the Treg cell lineage and act as a critical regulator of T-cell homeostasis^[33]. Humans and mice deficient in Foxp3 suffer from a fatal early-onset immune-mediated disorder characterized by T-cell dependent lymphoproliferation. In cancer immunology, Treg cells are critical for a tumor's ability to actively impede the anti-tumor immune response. Higher levels of Treg cells in the PDAC microenvironment are associated with poor prognosis in patients with PDAC^[21].

THE CANCER IMMUNITY CYCLE AND RELEVANT ISSUES IN PDAC

Elimination of cancer cells by Tc cells is the last stage in the cancer immunity cycle, but it requires maintenance of an elegantly delicate balance between the perception of non-self and the avoidance of autoimmunity. The proposed model of the cancer immunity cycle includes seven immunologic steps for killing tumor cells^[10,34]: (step 1) release of cancer cell antigens; (step 2) cancer antigen presentation by antigen presenting cells (APCs); (step 3) priming and activation of T cells; (step 4) trafficking of Tc cells to tumors; (step 5) infiltration of Tc cells into tumors; (step 6) recognition of cancer cells by Tc cells through T cell receptor (TCR) signaling; and (step 7) killing of cancer cells.

The immune escape mechanisms during these seven steps in PDAC are as follows^[10]: (step 1) low mutational load; (step 2) tumor-induced signal transducer and activator of transcription 3 signaling and impaired function of dendritic cells; (step 3) CTLA-4 signaling, reduced serum levels of stimulatory IL-2 and elevated levels of immune-suppressive tumor necrosis factor alpha, TGF- β 1, IL-10, and IL-1 β ; (step 4) preferential trafficking of Tregs to PDAC, attraction of Tc cell to the panstromal rather than the juxtatumoral compartment by the CXCL12 expression in pancreatic stellate cells; (step 5) reduced migratory ability of T-cells due to dense stroma; (step 6) downregulation of major histocompatibility complex (MHC) class I molecules; and (step 7) PD-1/PD-L1 signaling, infiltrating immune cells such as MDSC and M2-polarized macrophages.

IMMUNOTHERAPEUTIC DRUGS FOR PDAC

Allison JP and Honjo T won the 2018 Nobel Prize in Physiology or Medicine for their work on cancer immunotherapy. Immunotherapy using immune checkpoint inhibitors (anti-CTLA-4 and anti-PD-1 antibodies) represents a successful translation from gene discovery to the development of therapeutics^[35]. Current immunotherapy includes checkpoint inhibitors, adoptive T cell transfer therapy, and vaccines (Table 1). Unfortunately, the brilliant clinical results seen with immunotherapy across a wide range of malignancies has not been reproduced in the PDAC (Table 2)^[36]. Resistance of PDAC to immunotherapy has been attributed to the poor intrinsic antigenicity of the

Table 1 Potential immunotherapeutic agents for pancreatic cancer

Immunotherapeutics	Mechanisms		FDA approval
Ipilimumab	Antagonist antibody to CTLA-4 on T cells	CTLA-4: Suppressing the initiation of immune response	Other cancers
Pembrolizumab, nivolumab, cemiplimab	Antagonist antibody to PD-1 on T cells	PD-1: Suppressing the antitumor response of Tc cell	Yes ¹
Atezolizumab, durvalumab, avelumab	Antagonist antibody to PD-L1 on cancer cell or MDSC	PD-L1: A ligand of PD-1, promoting PD-1 signaling	Other cancers
Imiquimod	Agonist of TLR7 on MDSC or M2 macrophage	TLR7: Promoting macrophage polarization towards an M1 phenotype	Other cancers
Plerixafor (AMD3100), BL-8040	Antagonist of CXCR4 on T cells	CXCR4: Receptor of CXCL12, negatively regulating Tc cell immune function	Other cancers
Indoximod	Antagonist of IDO in MDSC or APC	IDO: Inducing tolerance to tumor-derived antigens in APC and inhibiting Tc cell	-
Imidazole-dioxolane	Antagonist of HO in M2 macrophage	HO: Suppressing Tc cell by producing carbon monoxide	-
APX005M, CP-870893	Agonist antibody to CD40 on APC, T cell, or M1 macrophage	CD40: Proinflammatory action	-
CAR T cells	Directly targeting cancer cells <i>via</i> reprogramming a patient's own T cells with a CAR that recognizes a specific antigen	Potential targets in pancreatic cancers: CEA, mesothelin, ROR1, EpCAM, HER2, MUC1	Other cancers
Cancer vaccines	Activating T cell <i>via</i> presentation by APC	GVAX ² , GV1001 (telomerase peptide vaccine)	Other cancers

¹All solid tumors with microsatellite instability.

²Allogeneic irradiated whole-cell tumor vaccine transfected with *granulocyte-macrophage colony-stimulating factor* gene. CTLA-4: Cytotoxic T lymphocyte-associated protein 4; PD-1: Programmed cell death 1; PD-L1: Programmed cell death ligand 1; TLR7: Toll-like receptor 7; MDSC: Myeloid-derived suppressor cell; CXCR4: C-X-C chemokine receptor type 4 or CD184; CXCL12: C-X-C motif chemokine 12; IDO: Indoleamine 2,3-dioxygenase; HO: Heme oxygenase; Tc cell: Cytotoxic T cell; APC: Antigen presenting cell; CAR: Chimeric antigen receptor; ROR1: Receptor tyrosine kinase-like orphan receptor 1; EpCAM: Epithelial cell adhesion molecule; HER2: Human epidermal growth factor receptor 2; MUC1: Mucin 1; FDA: United States Food and Drug Administration; CEA: Carcinoembryonic antigen; GVAX: Granulocyte-macrophage colony-stimulating factor-transfected pancreatic tumor vaccine.

tumor cells and defective antigen presentation, as well as a strongly immunosuppressive microenvironment enriched in MDSC and Treg cells^[36-38]. In 2018, the clinical practice guideline update of the American Society of Clinical Oncology (ASCO) for metastatic pancreatic cancer stipulated that the PD-1 immune checkpoint inhibitor pembrolizumab is recommended as second-line therapy for patients who have tested positive for mismatch repair deficiency or MSI-h^[39]. Other agents are also undergoing preclinical/clinical trials as combination therapies.

Anti-CTLA-4 antibodies

CTLA-4 has an important role in preserving normal immune function, as supported by the reports that mice deficient in CTLA-4 died of fulminant lymphoproliferative disorder^[13,40,41]. In the lymph node, a T cell normally recognizes a specific tumor antigen, which is presented by an APC such as a dendritic cell (Figure 1A). The T cell interacts with the APC *via* 1) TCR engagement with a MHC on the APC and 2) CD28 (a costimulatory signal) with B7 on the APC (Figure 1A). CTLA-4, a close homolog of CD28, is an intracellular protein in resting T cells. After T cell activation, CTLA-4 translocates to the cell surface and mediates inhibitory signaling into the T cell, *via* competitive inhibition of CD28, resulting in a pause in both proliferation and activation^[13,40].

Ipilimumab is a fully humanized IgG1 monoclonal antibody that inhibits CTLA-4. It is approved by the FDA for the treatment of melanoma and renal cell carcinoma. While durable tumor regressions after treatment with ipilimumab can occur in advanced melanoma, this can be accompanied by immune-related adverse events resulting from tissue-specific inflammation^[13]. The common adverse events include enterocolitis, inflammatory hepatitis, and dermatitis. Algorithmic use of corticosteroids or other immunosuppressants can readily control these adverse events

Table 2 Clinical outcomes of immunotherapies in advanced pancreatic cancer

Study drug	Ref.	Clinical setting	Therapeutic protocol	Study phase	Number of patients	Outcomes	Adverse events (Grade 3 or 4)
<i>Anti-CTLA-4 antibodies</i>							
Ipilimumab	Royal <i>et al</i> ^[42] , 2010	Locally advanced or metastatic	Ipilimumab only	II	27	ORR: 0%, but one delayed tumor regression after initial progression	11.1% (3/27; 1 fatal pneumonia, 1 confusion and lethargy, 1 hypophysitis)
Ipilimumab	Kamath <i>et al</i> ^[66] , 2020	Locally advanced or metastatic	Gemcitabine + Ipilimumab	Ib	21	ORR: 14% (3/21). PFS: 2.78 mo. OS: 6.90 mo	76.2% (16/21; elevated ALT, diarrhea, mostly hematologic toxicity)
<i>Anti-PD-1 antibodies and anti-PD-L1 antibodies</i>							
Pembrolizumab	Le <i>et al</i> ^[46] , 2017	Solid tumor with MSI-h	Pembrolizumab only	II	8 (all cancer 86)	ORR: 53% in solid tumor with MSI-h	N-A (mostly low grade)
Pembrolizumab	Weiss <i>et al</i> ^[68] , 2018	Metastatic	Gemcitabine + Nab-paclitaxel + Pembrolizumab	Ib/II	17	PFS: 9.1 mo. OS: 15.0 mo	70.6% (12/17)
Nivolumab	Wainberg <i>et al</i> ^[67] , 2020	Locally advanced or metastatic	Gemcitabine + Nab-paclitaxel + Nivolumab	I	50	ORR: 18%. PFS: 5.5 mo. OS: 9.9 mo	36.0% (18/50; peripheral neuropathy, hypokalemia, diarrhea, increased AST/ALT, mostly hematologic toxicity)
Durvalumab	Renouf, 2020 (abstract)	Metastatic	Gemcitabine + Nab-paclitaxel + Durvalumab + Tremelimumab <i>vs</i> Gemcitabine + Nab-paclitaxel	II	119 <i>vs</i> 61	ORR: 30.3% <i>vs</i> 23.0%. PFS: 5.5 mo <i>vs</i> 5.4 mo. OS: 9.8 mo <i>vs</i> 8.8 mo	N-A
<i>CAR T cell immunotherapy</i>							
Mesothelin-specific	Beatty <i>et al</i> ^[51] , 2018	Metastatic	Mesothelin-specific CAR T cells	I	6	Disease stabilized: 2 patients (33%) with PFS of 3.8 and 5.4 mo	0% (0/6)
<i>Vaccine-based immunotherapy</i>							
GV1001	Middleton <i>et al</i> ^[54] , 2014	Locally advanced or metastatic	Gemcitabine + Capecitabine <i>vs</i> Gemcitabine + Capecitabine with sequential GV1001 <i>vs</i> Gemcitabine + Capecitabine with concurrent GV1001	III	358 <i>vs</i> 350 <i>vs</i> 354	OS: 7.9 mo <i>vs</i> 6.9 mo <i>vs</i> 8.4 mo	13.1% <i>vs</i> 12.6% <i>vs</i> 12.4%
GVAX	Le <i>et al</i> ^[56] , 2019	Metastatic, previously treated	Cy/GVAX + CRS-207 <i>vs</i> CRS-207 <i>vs</i> Single-agent chemotherapy	Iib	73 <i>vs</i> 68 <i>vs</i> 72	OS: 3.7 mo <i>vs</i> 5.4 mo <i>vs</i> 4.6 mo	46.8% <i>vs</i> 36.8% <i>vs</i> 27.8%
GVAX	Wu <i>et al</i> ^[55] , 2020	Metastatic	GVAX + Ipilimumab after FOLFIRINOX <i>vs</i> FOLFIRINOX continuation	II	40 <i>vs</i> 42	PFS: 2.4 mo <i>vs</i> 5.55 mo. OS: 9.38 mo <i>vs</i> 14.7 mo	41.0% (16/39; adrenal insufficiency, hypophysitis, rash, diarrhea)

ORR: Objective response rate; OS: Overall survival (median); PFS: Progression free survival (median); GV1001: Telomerase reverse transcriptase catalytic subunit class II 16mer peptide vaccine; GVAX: Granulocyte-macrophage colony-stimulating factor-transfected pancreatic tumor vaccine; Cy: Cyclophosphamide; CRS-207: Live attenuated *Listeria monocytogenes* expressing mesothelin; PD-1: Programmed cell death 1; ALT: Alternative lengthening of telomeres; AST: Aspartate aminotransferase; CAR: Chimeric antigen receptor; CTLA-4: Cytotoxic T lymphocyte-associated protein 4; MSI-h: Microsatellite instability-high; PD-L1: Programmed cell death ligand 1.

without any apparent loss of antitumor activity^[13]. Endocrinopathies due to inflammation of the thyroid, pituitary, and adrenal glands are infrequent developments that can require lifelong hormone replacement.

Royal *et al.*^[42] reported a phase II trial that evaluated the efficacy of ipilimumab for advanced PDAC^[42]. No responders were observed that met the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. However, a delayed regression of tumor was found in one subject with initial progressive disease.

Anti-PD-1/anti-PD-L1 antibodies

The PD-1 inhibitory receptor has a dominant role in the maintenance of peripheral immune tolerance, although its name is attributed to its initially identified ability to induce apoptosis (programmed cell death)^[13,40,43,44]. PD-1 is expressed at the cell surface of activated T cells (Figure 1B)^[43]. PD-L1, which is the ligand of PD-1, is expressed on the surface of cancer cells, MDSCs, or M2 macrophages within the tumor microenvironment^[43]. Engagement of PD-1 with PD-L1 within a tumor causes PD-1 to inhibit kinase signaling pathways that normally lead to T-cell activation. The result is inhibition of Tc cell activity within the tumor and evasion of immune surveillance by the cancer cells.

Pembrolizumab, nivolumab, and cemiplimab are monoclonal antibodies that target PD-1. Pembrolizumab and nivolumab may be interchangeable alternatives that target their approved indications^[45]. Atezolizumab, durvalumab, and avelumab are monoclonal antibodies that target PD-L1. They are approved by the FDA for the treatment of various tumors, which are classified into two categories: (1) high response rate (53%-87%), including Hodgkin's disease, desmoplastic melanoma, Merkel cell carcinoma, and MSI-h cancer; and (2) intermediate response rate (15%-40%), including skin melanoma, non-small cell lung cancer, head and neck squamous cell cancer, gastroesophageal cancer, bladder and urinary tract cancer, renal cell cancer, and hepatocellular carcinoma. Adverse events associated with single-agent anti-PD-1 or anti-PD-L1 antibodies are uncommon, but they can include the development of fatigue, diarrhea, rash, and pruritus in 15% to 20% of patients^[13]. As with anti-CTLA-4 antibodies, endocrinopathies due to inflammation of the thyroid, pituitary, and adrenal glands can be infrequent development that require lifelong hormone replacement. Serious toxicities due to visceral organ inflammation are very rare, but these can affect any organ, including the brain, meninges, and heart^[13].

Le *et al.*^[46] reported that treatment with pembrolizumab accomplished objective radiographic responses in 53% of patients and achieved complete responses in 21% of 86 patients with 12 different cancer types with MSI-h (pancreas, $n = 8$), who had received at least one prior therapy and had evidence of disease progression^[46]. The researchers also suggested that the large proportion of mutant neoantigens (tumor mutational burden) in cancers with MSI-h lead the tumor responsive to immune checkpoint blockade, regardless of the origin of cancer^[46]. Despite the small population of pancreatic cancers in this study, the ASCO guideline 2018 included pembrolizumab as a second-line therapy for patients with metastatic PDAC who have tested positive for mismatch repair deficiency or MSI-h^[39]. Therefore, routine testing for MSI-h, using immunohistochemistry, polymerase chain reaction, or next-generation sequencing (NGS), is recommended for patients with PDAC who are considered candidates for checkpoint inhibitor therapy^[39]. However, clinicians also must remain aware that the reported incidence of MSI-h in patients with PDAC was very low (< 1%)^[47,48].

CAR T cell immunotherapy

CAR T cells can be used in one form of adoptive T cell transfer^[12]. Adoptive T cell transfer therapy makes good use of the patient's own immune system^[49]. CAR is a fusion protein composed of an extracellular part derived from an antibody and intracellular signaling molecules originated from T cell signaling proteins^[12]. After the harvest of an individual patient's own T cells, CAR replaces one part of the TCR so that identifies a specific tumor antigen (Figure 2)^[49]. After *ex vivo* expansion, the CAR T cells are re-infused into the patient, allowing the patient's own T cells to target a specified antigen within the context of the patient's own MHC^[49]. Based on the durable clinical responses of treatment-refractory B cell malignancies, anti-CD19 CAR T cell therapy has recently been approved by the FDA for the treatment of refractory pre-B cell acute lymphoblastic leukemia and diffuse large B cell lymphoma. Adverse events of CAR T cell therapy include cytokine release syndrome and neurotoxicity^[12].

CAR targets studied in pancreatic cancer include carcinoembryonic antigen, mesothelin, receptor tyrosine kinase-like orphan receptor 1, epidermal growth factor receptor, epithelial cell adhesion molecule, CD133, mucin 1, human epidermal growth factor receptor-2, etc^[49,50]. Unfortunately, most patients with advanced PDAC have

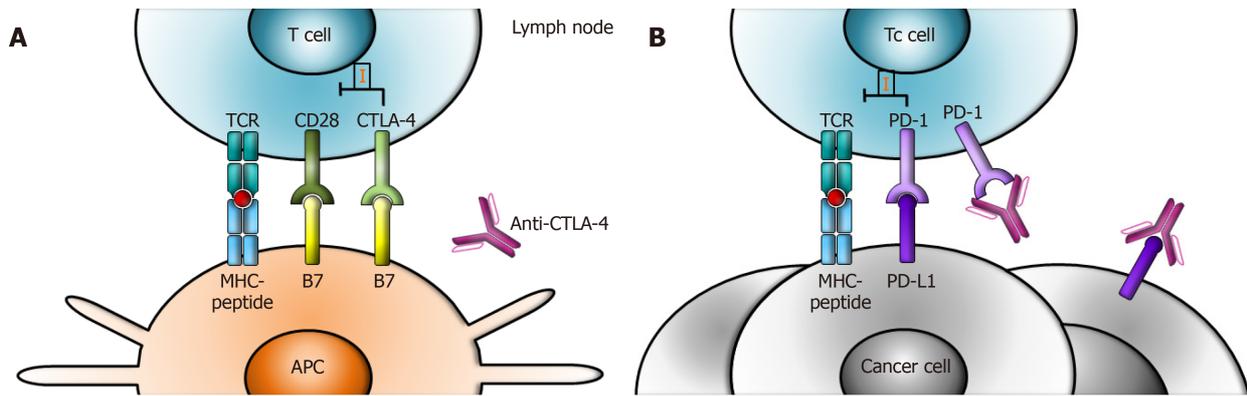


Figure 1 T cell checkpoints and their inhibitors to induce anti-cancer immunity. A: cytotoxic T lymphocyte-associated protein 4 (CTLA-4) in priming and activation of T cell in a lymph node. A T cell normally recognizes a specific tumor antigen, which is presented by an antigen presenting cell in the context of a major histocompatibility complex molecule in addition to the costimulatory signal B7. CTLA-4 is a negative regulator of costimulation that mediates inhibitory signaling into the T cell *via* competitive inhibition of CD28. CTLA-4 pathway to suppress initiation of an immune response can be blocked with anti-CTLA-4 antibodies (e.g. ipilimumab); B: Programmed cell death 1 (PD-1) in recognition and killing of cancer cell by cytotoxic T cell within a tumor. PD-1 is expressed on activated T cell after the triggering of the T cell receptor. Engagement of PD-1 with programmed cell death ligand 1 (PD-L1) mediates inhibitory signaling into the cytotoxic T cell. PD-1 pathway to suppress antitumor T cell responses can be blocked by anti-PD-1 (e.g. pembrolizumab) or anti-PD-L1 antibodies (e.g. atezolizumab). CTLA-4: Cytotoxic T lymphocyte-associated protein 4; APC: Antigen presenting cell; I: Inhibitory signaling; PD-1: Programmed cell death 1; PD-L1: Programmed cell death ligand 1; TCR: T cell receptor; MHC: Major histocompatibility complex; MDSC: Myeloid-derived suppressor cell; M2: M2-polarized macrophage.

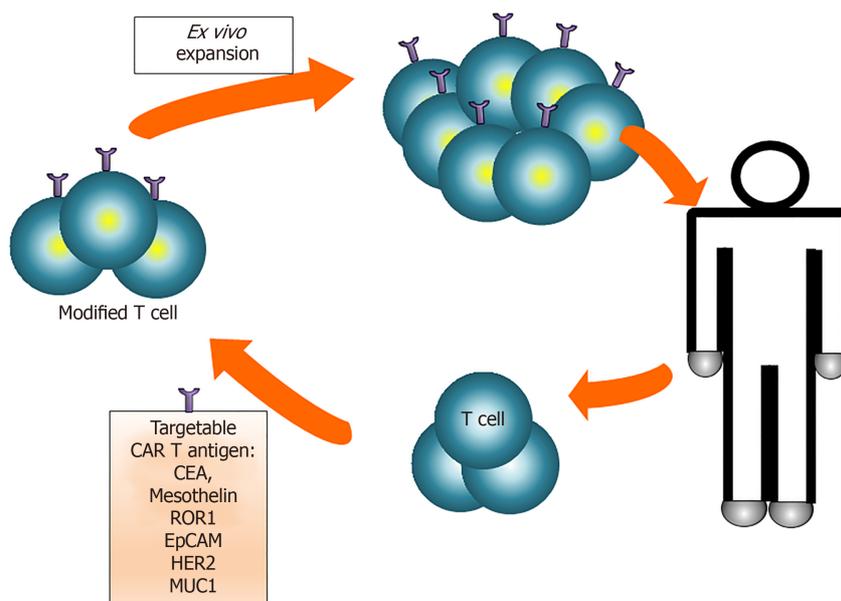


Figure 2 Illustrations of chimeric antigen receptor T cells immunotherapy. CEA: Carcinoembryonic antigen; ROR1: Receptor tyrosine kinase-like orphan receptor 1; EpCAM: Epithelial cell adhesion molecule; HER2: Human epidermal growth factor receptor 2; MUC1: Mucin 1; CAR: Chimeric antigen receptor.

failed to respond well to CAR T cell immunotherapy^[49,51].

Vaccine-based immunotherapy

Vaccine-based immunotherapy is an immunotherapeutic strategy that stimulates the tumor-specific immunity of patients by administration of a tumor antigen^[52,53]. Antigens can be delivered in the form of whole tumor cells, whole proteins, peptides, DNA, RNA, or antigen-pulsed dendritic cells^[52]. Vaccination induces many immunologic responses, including infiltration of effector T cells and reduction of infiltration of MDSC and Treg cells, as well as antibody formation and tumor killing mediated by complement-dependent cytotoxicity^[53]. However, cancer vaccines have yet to prove effective as a treatment for pancreatic cancer. GM-CSF-transfected pancreatic tumor vaccine (GVAX), an allogenic whole cell vaccine generated from a PDAC cell line genetically modified to express GM-CSF, and telomerase peptide

vaccine GV1001 gave no survival benefit in patients with advanced pancreatic cancer^[54-56]. Vaccine-based immunotherapy might be an attractive approach as a post-surgical adjuvant treatment^[52]. Zheng *et al*^[57] recently reported that GVAX-induced intratumoral lymphoid aggregates correlated with survival following treatment with a neoadjuvant and adjuvant vaccine in patients with resectable PDAC^[57].

Personalized vaccines for cancer immunotherapy can be viewed as promising because every cancer has its own distinctive set of mutations, and only a small fraction is shared between patients^[58]. With the advances in NGS technology for rapid mapping of the mutations within a genome, on-demand production of a customized vaccine for an individual patient kicked off the clinical trials using personalized vaccines^[58].

RESPONSE CRITERIA FOR USE IN TRIALS TESTING IMMUNOTHERAPEUTICS

The response to therapy, which is defined as changes in tumor burden after treatment, is a mainstay in the evaluation of cancer therapeutics and provides key information about the objective response and disease progression^[59]. In 2000, the RECIST working group simplified the WHO response criteria and proposed the "RECIST criteria", which were further refined to RECIST version 1.1 in 2009^[60]. In the present era, which is characterized by a plethora of trials testing immunotherapeutics, clinicians should recognize that the pattern of response may differ between immunotherapies and chemotherapeutic drugs^[40,59]. Some patients who were treated with immunotherapeutics and whose disease met the criteria for disease progression based on the RECIST guideline were noted to have late, but deep and durable, responses. Early investigators termed this unique response pattern "pseudoprogression"^[59].

To capture the potentially beneficial effects of immunotherapeutics, immune-related response criteria were first proposed by investigators in 2009 and revised in 2013^[61,62]. The need to standardize and validate response criteria led the RECIST working group to propose a modified RECIST 1.1 for immune-based therapeutics (termed iRECIST) in 2017^[59]. The category of new lesions is an important difference between RECIST 1.1 and iRECIST. According to RECIST 1.1, new lesions result in progression without the necessity of size measurement. In contrast, iRECIST states that new lesions will be categorized as unconfirmed progression, and then followed^[59]. Confirmed progression in iRECIST is only assigned if additional new lesions appear at next assessment or an increase in size of new lesions is seen (≥ 5 mm for sum of new lesion target or any increase in new lesion non-target)^[59]. According to iRECIST, if a new lesion is identified and the patient is clinically stable, treatment should be continued until the next assessment (≥ 4 wk later); this next imaging assessment should be no longer than 8 wk later to ensure that patients remain fit for salvage therapies^[59]. A longer timeframe before the next assessment might be reasonable if pseudoprogression is well described in the tumor type, especially if no effective salvage therapies are available; however, this should be justified in the trial protocol.

COMBINATION THERAPIES

Clinical trials that have used single immunotherapeutic agents to find a magic bullet that will kill PDAC cancer cells have mostly been disappointing. However, immunotherapy may provide a novel opportunity for treatment of patients with PDAC when combined with other immunotherapeutic agents, targeted therapies, stromal modulating agents, microbial ablation, chemotherapy, radiotherapy, chemoradiotherapy, or multi-way combination therapies^[37,49,63-65]. As anti-PD-1 agents showed efficacy in some type of PDAC, the anti-PD-1/anti-PD-L1 agents may serve as a backbone for the combination therapies in the field of PDAC immunotherapy. Combinations of anti-PD-1/anti-PD-L1 agents with therapies against 240 different targets of many types of cancers are currently being assessed, although only two anti-PD-1 combination therapies have been approved to date by the FDA^[65].

Kamath *et al*^[66] recently reported a similar response rate of gemcitabine and ipilimumab in advanced pancreatic cancer, compared with gemcitabine alone^[66] (Table 2). Wainberg *et al*^[67] reported a similar response rate of gemcitabine, nab-paclitaxel, and nivolumab in advanced pancreatic cancer^[67], but Weiss *et al*^[68] reported a slightly improved response rate of gemcitabine, nab-paclitaxel, and pembrolizumab in metastatic pancreatic cancer, compared with gemcitabine and nab-paclitaxel

chemotherapy^[68]. According to Wu *et al*^[55], GVAX and ipilimumab after FOLFIRINOX resulted the lower overall survival than continuation of FOLFIRINOX chemotherapy in patients with metastatic pancreatic cancer^[55].

FUTURE PROSPECTS

As pembrolizumab was associated with considerable objective radiographic responses in PDAC with MSI-h^[46], research for combinations of anti-PD-1 with other immune checkpoint inhibitors, CAR T cells, pathway inhibitors, microenvironment modulating agents, chemotherapy, or multiple combination therapies could be tried. For priming the immune system, use of various cancer vaccines may initiate the anti-tumor immune response in this lethal cancer. Although GVAX failed to improve the overall survival, other kind of vaccines might be effective in combination therapies by promoting the recruitment of T cells, resultantly enhancing the effect of immune check point inhibitors or other agents^[48]. For expecting future management of PDAC, attentions should be paid ongoing clinical trials. From a plethora of ongoing clinical trials, well-organized tables regarding hopeful trials are also available in other review articles^[48,69].

CONCLUSION

Pancreatic cancer is a highly lethal cancer and has the lowest 5-year survival rate because of its aggressive invasion and its resistance to systemic therapies. Pancreatic cancer is capable of immune escape, through various mechanisms including the immunosuppressive dense fibrotic tumor microenvironment and overall low tumor mutational burden. Immunotherapy has the potential to eliminate cancer cells by restoring cancer immunity. Despite brilliant results seen with immunotherapy across a wide range of malignancies, immunotherapeutics for pancreatic cancer are currently not standard of care. Only anti-PD-1 antibodies have been approved by the United States FDA for patients with pancreatic cancer who have tested positive for microsatellite instability. Combination therapies with other immunotherapeutic agents, targeted therapies, stroma-modulating agents, chemotherapy, or multi-way combination therapies may provide treatment opportunities for patients with pancreatic cancer. We remain hopeful that aggressive pancreatic cancer will become one type of chronic diseases that is controllable by immune-based therapy.

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