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Understanding the immune response and the current landscape of immunotherapy in pancreatic cancer

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive tumor with high lethality. Even with surgery, radiotherapy, chemotherapy, and other locoregional or systemic therapies, the survival rates for PDAC are low and have not significantly changed in the past decades. The special characteristics of the PDAC's microenvironment and its complex immune escape mechanism need to be considered when designing novel therapeutic approaches in this disease. PDAC is characterized by chronic inflammation with a high rate of tumor-associated macrophages and myeloid-derived suppressor cells and a low rate of natural killer and effector T cells. The pancreatic microenvironment is a fibrotic, microvascularized stroma that isolates the tumor from systemic vascularization. Immunotherapy, a novel approach that has demonstrated effectiveness in certain solid tumors, has failed to show any practice-changing results in pancreatic cancer, with the exception of PDACs with mismatch repair deficiency and high tumor mutational burden, which show prolonged survival rates with immunotherapy. Currently, numerous clinical trials are attempting to assess the efficacy of immunotherapeutic strategies in PDAC, including immune checkpoint inhibitors, cancer vaccines, and adoptive cell transfer, alone or in combination with other immunotherapeutic agents, chemoradiotherapy, and other targeted therapies. A deep understanding of the immune response will help in the development of new therapeutic strategies leading to improved clinical outcomes for patients with PDAC.

Key Words: Pancreatic cancer; Immunity; Immune evasion; Tumor microenvironment; Immunotherapy; Cancer vaccines

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Core Tip: Immunotherapy has demonstrated effectiveness in treating several solid tumors and has become a major revolution in oncology. In pancreatic ductal adenocarcinoma, however, the outcomes continue to be poor due to its special immune response and microenvironmental characteristics. In this review, we summarize the most important concepts of the immune system and the current landscape of immunotherapy in pancreatic cancer.

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INTRODUCTION

Pancreatic ductal adenocarcinoma cancer (PDAC) derives from pancreatic glandular tissue and is considered the fourth most lethal malignant tumor worldwide, with high mortality and poor prognosis[1]. The aggressive nature of PDAC is the result of a multifactorial condition related to its desmoplastic stroma and characteristic tumor microenvironment (TME), the ability to evade the immune response, the low tumor mutational burden (TMB) and the lack of effective treatments[2].

Despite the use of various approaches and therapies such as surgical resection, radiotherapy, systemic chemotherapy and the combination of these therapies[3], 80% of such patients will die within a year of the diagnosis[4]. Even for patients with resectable disease who undergo R0 pancreatic surgery, the 5-year survival rate is less than 20%[5,6], and the 5-year overall survival (OS) is lower than 7% for those with metastatic PDAC[7]. Novel therapeutic strategies such as adjuvant modified FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin) have improved postoperative survival rates[8]. For advanced and metastatic PDAC, chemotherapy is the only treatment option. Despite the new chemotherapy regimens developed over the past few years (FOLFIRINOX and gemcitabine plus nab-paclitaxel), however, the median OS is still under 12 mo[1,8]. Most of the driver mutations identified in PDAC lack targeted therapies. Nevertheless, patients might benefit from platinum-based chemotherapy and poly (ADP-ribose) polymerase (PARP) inhibitors in the case of BRCA1/2 mutation[9], immune checkpoint inhibitors in microsatellite instability[10] and tyrosine-kinase inhibitors for patients harboring neurotrophic-tropomyosin receptor kinase (NTRK) gene fusions[11], although the improvement in survival is not as successful as in other tumors. Even with all these advances, the OS for PDAC has hardly improved in recent decades.

Immunotherapy is a classic treatment approach and has been recognized since 2017 as the fourth pillar of treatment for many solid tumors[12]. A high number of preclinical and clinical studies are evaluating the efficacy of immunotherapeutic strategies in PDAC, including immune checkpoint inhibitors, cancer vaccines, and adoptive cell transfer, combined with other immunotherapeutic agents, chemoradiotherapy or other molecularly targeted agents. However, this new strategy still fails to meet the clinical needs of patients with PDAC, a consequence of the complex immune escape mechanisms, which need to be understood to improve the efficacy of new therapies.

In this review, we summarize the immune response mechanisms, the current landscape and the limitations of immunotherapy in PDAC.

IMMUNE RESPONSE IN PANCREATIC CANCER

The immune system and inflammatory state involve numerous interactions with premalignant and malignant lesions. While chronic inflammation induced by the immune system is associated with tumor growth[13], tumors cause tissue destruction and trigger inflammatory signals leading to the recruitment of cells of the innate immune system such as natural killer (NK), T cells, macrophages, and dendritic cells

(DCs)[13]. Inflammation is characterized by supporting hallmarks capabilities that contribute to tumor progression by providing cytokines, chemokines, proteases, and growth and proangiogenic factors; encouraging angiogenesis and tissue remodeling, assisting in the invasion and metastasis and ultimately driving local and systemic immune suppression[13].

In an effort to understand the dynamics of the immune response from preinvasive pancreatic intraepithelial neoplasia (PanIN) to invasive and metastatic PDAC, a study with genetically engineered *KRAS* and *p53* mutant mice showed that immune system cells with suppressive properties are involved from the earliest stages of tumorigenesis. The *RAS* oncogene induces inflammation and immune suppression in the microenvironment, and both carry immune privilege in the tumor[14]. The predominant cells in the tumor stroma are immunosuppressive leukocytes that weakens the antitumor functions of lymphocytes infiltrating the pancreas and promote disease progression[15]. In contrast, many other solid tumors harbor a larger infiltration of effector T cells, which has been associated with enhanced clinical outcomes [14].

Immune system cells in pancreatic ductal adenocarcinoma

The most common immune cells in the tumor microenvironment (from PanIN to PDAC) include tumor-associated macrophages (TAM), myeloid-derived suppressor cells (MDSC), neutrophils, regulatory T cells (Treg), a smaller number of effector T cells and, rarely, NK cells[13-15].

TAMs and MDSCs are innate immune cells that play a dual role in PDAC and are involved in cancer cell recognition and antitumor response but also lead to chronic inflammation[16,17]. Macrophages are predominant in the initial stages of the disease, but the ratio of TAMs and MDSCs becomes similar as the disease progresses[15]. There are very few lymphocytes in the tumor; CD4+ T cells, along with a high portion of Tregs, are the most frequent. NK and CD8+ T cells are extremely rare at any stage [15].

Tumor-associated macrophages

Two types of TAMs have been identified: M1 and M2 macrophages. M1 macrophages secrete proinflammatory cytokines with antineoplastic effects, while M2 macrophages release cytokines that lead to tumor progression[18,19]. Macrophages are the most common immune cells in the tumor microenvironment at the early stage. Several reports have shown an inverse correlation between the prognosis and M2 TAM infiltration in various tumors, including PDAC[20,21].

TAMs produce cytokines, proteases and metabolites, such as indoleamine dioxygenase and reactive oxygen species, which inhibit T-cell activity against tumor and attract Tregs to the tumor site[22]. Moreover, TAMs facilitate tumor angiogenesis by releasing pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and participate in matrix remodeling to facilitate invasion and metastasis[23].

Myeloid derived suppressor cells

MDSCs are a heterogeneous group of immature cells divided into polymorphonuclear (PMN-MDSC) and monocytic (M-MDSC), resembling neutrophils and monocytes, respectively[24,25]. Myeloid cells are more frequent in the advanced stages of PDAC, when the number of these cells is comparable to TAMs'. MDSCs inhibit the innate antitumor immunity[26].

MDSCs have a variety of mechanisms to attenuate immune response. They inhibit the antigen-specific response of CD4+ and CD8+ T cells. Some of these mechanisms occur through direct cell-to-cell contact between MDSCs and lymphocytes with the participation of programmed death-ligand 1 (PD-L1) and programmed death-1 (PD-1). MDSCs therefore induce the suppression of T-cell activation and self-tolerance[26]. In addition, MDSCs suppress the proliferation, cytokine production, and cytotoxic function of T cells[27]; decrease T-cell receptor signaling[28]; and induce apoptosis of intratumor T cells[28]. Furthermore, MDSCs induce Treg expansion through interleukin (IL)-10[29], resulting in additional suppression of T-cell function. As with TAMs, an increase in MDSCs in patients with cancer is related to high levels of VEGF [30].

Natural Killer cells

NK cells are an important immune component in controlling the antitumor immune response. These immune cells can interact with DCs, macrophages, T cells and endothelial cells through cell-to-cell contact and secreting cytokines[31]. A number of studies have found that natural killer (NK) cells are positively correlated with survival

in patients with PDAC[32]. However, PDAC is characterized by a very low count of NK cells in the tumor site ($< 0.5\%$)[33]. Furthermore, the antitumor effect of NK cells decreases by the action of pancreatic stellate cells[34] and the expression of IL-10, transforming growth factor beta (TGF- β), indoleamine 2,3-dioxygenase (IDO), and matrix metalloproteinases (MMPs)[35].

Tumor associated Neutrophils

Tumor associated neutrophils (TANs) are typically localized at the periphery of the tumor site in early stages of the disease and infiltrate the center of the tumor in advanced stages. The neutrophil-to-lymphocyte ratio (NLR) has been studied as a predictor, and high TAN counts are correlated with poor prognoses[36-38]. However, the value of the NLR with regard to prognosis and survival prediction requires further validation.

There are two types of TANs: N1 and N2 which have different functions[39]. N1 TANs are proinflammatory and releases IL-12, tumor necrosis factor (TNF)- α and other immunostimulatory cytokines involved in the migration and activation of CD8 $^{+}$ T cells[40]. N2 TANs are immunosuppressive and promote angiogenesis, invasion and metastases. These tumor-promoting activities are mediated by hepatocyte growth factor (HGF), oncostatin M, reactive oxygen species (ROS), reactive nitrogen species (RNS), matrix metalloproteinase (MMPs), and neutrophil elastase (NE)[39].

T cells

PDAC presents a variable number of T cells, encompassing several T-cell subpopulations. The immunosuppressive microenvironment, compounded by fibroblast and desmoplastic stroma, prevents T-cell infiltration and influences their spatial distribution in the tumor site[41]. CD4 $^{+}$ and CD8 $^{+}$ T cells have specific regulation, produce several cytokines, and have different functions in immunity[42]. Consequently, the effects of T cells in PDAC depend on the subpopulation type, their spatial distribution, and macrophage infiltration. A high infiltration of CD4 $^{+}$ and CD8 $^{+}$ T cells, low infiltration of Treg cells, and high ratio of M1/M2 macrophages are therefore associated with greater survival in PDAC[43,44].

CD4 $^{+}$ lymphocytes are differentiated into T helper (Th) 1, Th2, Th17 and Treg subpopulations. Th1 produces interferon gamma (IFN- γ) and cytotoxic molecules that support cellular type I immunity (priming, activation and recruitment of cytotoxic T lymphocytes, M1 macrophages and NK cells) that attack intracellular pathogens and tumors immunity[45]. Th2 produces IL-4, IL-5 and IL-3, participates in humoral type II immunity (inducing M2 macrophages) and contributes to allergy and asthma[45]. Th2 is predominant in PDAC and is associated with disease progression[46] and shorter OS[47]. Th17 produces IL-17, IL-21 and IL-22 and protects against extracellular bacterial and fungal infections[48]. Oncogenic *KRAS*, expressed in pancreatic cells, induces the recruitment of Th17 cells into the TME[49]. Th17 and IL-17 are involved in PDAC progression[49]. A high proportion of Th17 cells in tumor site is correlated with shorter OS and distant disease.

Regulatory T cells or suppressor T cells are a subpopulation of CD4 $^{+}$ lymphocytes that infiltrate the tumor. The main function of Treg in healthy patients is to maintain tolerance to self-antigen and prevent autoimmune disease[50]. Treg counts increases from PanIN to advanced PDAC[15]. In case of PDAC, Tregs have differing roles depending on the tumor stage. Tregs promote tumorigenesis by suppressing the cytotoxic function of T cells, IFN- γ and IL-2, induced by tumor antigens[15]. In contrast, Tregs can delay tumor progression by assessing the suppressive myeloid cells[51]. Tregs are associated with worse prognosis and decreased survival[52].

CD8 $^{+}$ T cells, also Known as cytotoxic T lymphocytes and effector T lymphocytes, produce IFN- γ , TNF and cytotoxic molecules against tumor cells and protect from cancer recurrence[53]. CD8 $^{+}$ T cells are scarce in PDAC.

T cell evasion

The most well-known mechanism of immune tolerance in cancer is the exhaustion of effector T cells (CD8 $^{+}$ T lymphocytes), produced by the binding of cytotoxic T lymphocyte antigen 4 (CTLA-4) to CD80 and of PD-L1 (CD86) to PD-1. However, effector T lymphocytes are scarce in pancreatic cancer, and the inflammatory immune reaction develops early, suppressing the development of an adaptative immune response.

T cell evasion in PDAC has been describe as a 4-step process[14,15]: 1) Induction: mutations in oncogenes (*i.e.*, *KRAS*) and tumor suppressor genes initiate the process of tumorigenesis from normal pancreatic cells to PDAC. 2) Inflammation: PanIN, a

preinvasive lesion, produces soluble factors inducing local inflammation and recruitment of immune cells in the tumor site. 3) Immunosuppression: chronic inflammatory reaction and enrollment of TAMs, MDSCs and Treg cells produce immunosuppressive cytokines and suppressive response with cell-to-cell contact. Macrophages and suppressive T cells prevent effector T cells from entering the TME[54], while cytokines such as IL-10 and TGF inactivate the few effector T cells present in TME[55]. This condition prevents an efficient adaptive response against the tumor. 4) Immune Privilege: in the advanced stage of the disease, immune evasion persists, and the TME becomes a site of immune privilege for pancreatic tumor cells.

Tumor microenvironment: A barrier for immunotherapy

The PDAC microenvironment is a classical barrier involved in tumor progression[56], and low microvascular density hinders the diffusion of therapeutic agents[57,58]. This fibroinflammatory structure is a mixture of immune cells, malignant cells, and a dense desmoplastic stroma, which includes fibroblasts, blood vessels, and pancreatic stellate cells[59,60]. The stroma is a traditional characteristic of PDAC that participates in tumor growth, vascularization, drug diffusion, resistance to treatment, and metastasis[61]. Tumor cells and stromal cells undergo into a continuous change throughout the transformation process from a healthy pancreatic tissue to an invasive malignance[13]. TME plays a key role in this immunosuppression and presents similar characteristics in both primary and metastatic lesions[62].

Based on the biological, prognostic, and predictive characteristics, it is possible to differentiate two molecular subtypes (classical and basal-like)[63-65] and two stromal subtypes of PDAC (normal and activated)[66]. The basal-like subtype is associated with an activated stroma and poor prognosis[64,65]. Patients with the activated stromal PDAC subtype have a poorer prognosis compared with the normal stromal subtype, presenting a median OS of 15 *vs* 24 mo, respectively[66]. Activated stroma is associated with a greater presence of macrophages and activated fibroblasts, both responsible for poor clinical outcomes[66]. Modulating the TME would possibly redirect the immune system to eliminate the tumor, achieving greater efficiency in antitumor therapies.

Tumor mutational burden and mismatch repair deficiency: Assistance for immunotherapy

TMB is defined as the total number of nonsynonymous mutations per coding area of a tumor gene[67]. A high number of somatic mutations produces and releases neoantigens in the TME which lead to increase in inflammatory cytokines and effector T cells[2,10,68]. A high TMB therefore stimulates the efficacy of immunotherapy[67,69]. PDAC is characterized by low immunogenicity and low TMB (1 mutation/megabase) compared with other tumors such as melanoma (10 mutations/megabase)[67] and lung or bladder cancer (just under 10 mutations/megabase)[70].

There is a known association between mismatch repair deficiency (dMMR) and high TMB, and PDAC is not an exception[71]. dMMR represents a loss of function of the mismatch repair (MMR) pathway, a DNA repair pathway that plays a key role in maintaining genomic stability. Random mutations occurring in small repetitive elements define microsatellite instability (MSI)[72]. dMMR is defined as the loss of expression of one or more of the MLH1, MSH2, MSH6, and PMS2 proteins. Characteristically, dMMR is correlated with high TMB[72] and increased effector T cells in tumor site[63]. A high MSI status, an emerging predictor of immunotherapy response in PDAC, has a prevalence of 0.3-1.3% in this tumor type[73]. Patients with this condition present prolonged survival rates[71,74]. Neoantigens must be presented by antigen-presenting cells (APCs) to achieve a T-cell response and, in the case of PDAC, DCs (the major APCs), are usually immature or scarce, causing weakened T-cell activation[75].

LANDSCAPE OF IMMUNOTHERAPY IN PANCREATIC DUCTAL ADENOCARCINOMA

Our understanding of the immune response in cancer is still incomplete and continues to be investigated, with the reported relationships between the various cell populations and microenvironment composition[59,60] the basis for the development of immune-based therapies in PDAC. The combination of several immune strategies, such as checkpoints inhibitors, immune checkpoints inhibitors or vaccines plus

chemotherapy, and the use of adoptive cellular therapy are some of these new approaches[76].

Immune checkpoints agents

Whereas immune checkpoint inhibitors have proven their efficacy in many tumors, they have failed to do so in PDAC due to its low immunogenicity and low TMB[67]. These inhibitors help to interrupt the intratumoral T-cell dysfunction and provide the block of the overexpressed receptors involved in its exhaustion such as PD-1 and CTLA-4[77]. The union between PD-L1 or PD-L2 and PD-1 induces the cessation of T-cell effector functions causing a suppression in T-cell motility[78], an antagonization of T cell receptor (TCR) signaling[79] and a suppression in gene transcription[80]. PD-L1 expression is therefore inversely correlated with survival. Thus, anti-PD-L1 and anti-PD-1 therapies have been shown to reduce tumor volume in mice that were subcutaneously injected with a murine PDAC cell line[81].

Antibody anticytotoxic T lymphocyte antigen-4

Several phase II clinical trials in PDAC have been developed using antibodies against CTLA-4, such as Ipilimumab[82] and Tremelimumab[83] as single agents; however, these studies have not achieved an impact in OS[82,83]. Ipilimumab in a phase II trial (NCT00112580) of pretreated patients with locally advanced and metastatic pancreatic cancer showed a median OS of 4.5 mo, with no responders except for one patient who had a delayed objective response. A phase II trial of Tremelimumab (NCT02527434) in metastatic pancreatic cancer had a median OS of 4 mo (95%CI 2.83-5.42), with 18 out of 20 patients with progressive disease.

Antibody anti-programmed death-1

The efficacy of pembrolizumab in MSI-H PDAC has been reported in the phase II NCT02628067 study. The OS and progression-free survival (PFS) were 4 mo and 2.1 mo, respectively[76], highly disappointing results compared with those obtained in other tumors such as colorectal cancer in which a PFS of 16.5 mo was reported in the KEYNOTE-177 trial[84]. We do not have results for nivolumab or pembrolizumab as single agents in microsatellite stable tumors.

Antibody anti-programmed death-ligand 1

A phase I/II clinical trial (NCT03829501) assessing the efficacy of atezolizumab in advanced PDAC and other tumors refractory to first-line treatment is currently ongoing.

Combination of immune checkpoints agents

The combination of anti-PD-1/anti-PD-L1 and anti-CTLA-4 might have additive or synergistic activity[85]. In fact, the combination has shown enhanced activity in certain tumor types such as melanoma and non-small cell-lung cancer[85]. Several clinical trials have therefore sought to assess the efficacy of this combination.

Durvalumab alone or in combination with tremelimumab for patients with previously treated metastatic PDAC (NCT 02558894) did not achieve any improvement in OS. The combination achieved a median of 3.1 mo, while durvalumab alone achieved 3.6 mo[85]. However, the evaluation of the combination of other immunotherapy agents such as nivolumab and ipilimumab (NCT01928394) is still ongoing, with no results posted yet[86]. Table 1 Lists other immunotherapy agents that have been employed in treating PDAC.

Combination of immune checkpoints and chemotherapy

It has been suggested that the efficacy of immune checkpoint inhibitors could improve when combined with chemotherapy, the latter acting by activating the intratumoral immune response when inducing immunogenic cell death. This type of cell death is characterized by a necrolytic release of danger signals that can modify the stroma, change cytokine rates, reduce the presence of suppressive cells such as MDSCs and Tregs, promote the expression of molecules of the major histocompatibility complex (MHC) in cancerous cells and stimulate DC maturation[87]. In animal models, a synergetic effect has been observed between the combination of gemcitabine and anti-PDL1[88].

Several clinical trials have investigated the combination of immune checkpoint inhibitors and chemotherapy in PDAC. Table 2 Lists the main clinical trials in this field.

Table 1 Clinical trials on pancreatic ductal adenocarcinoma using immunotherapy

| National clinical trial number | Sample | Phase | Settings | Drug | Results |
|--------------------------------|--------|-------|---|---|---|
| NCT00112580 | 82 | II | Advanced; Metastatic; Any line | Ipilimumab | No improvement in survival rate |
| NCT02527434 | 64 | II | Advanced; Metastatic; ≥ Second line | Tremelimumab | OS 4 m (95%CI: 2.83-5.42) |
| NCT02558894 | 65 | II | Metastatic; ≥ Second line | Tremelimumab + Durvalumab vs Durvalumab alone | OS 3.1 m (95%CI: 2.2-6.1) Combination therapy; OS 3.6 m (95%CI: 2.7-6.1) Durvalumab alone |
| NCT00112580 | 27 | II | Advanced; Metastatic; ≥ Second line | Ipilimumab | No improvement in survival rate |
| NCT03379259 | 14 | I | Advanced (PDAC and other tumors); ≥ Second line | Anti-PD-L1 (BMS-936559) | No improvement in survival rate |
| NCT01928394 | 1131 | I/II | Advanced (PDAC and other tumors) Any line | Nivolumab ± Ipilimumab | Ongoing |
| NCT03829501 | 412 | I/II | Advanced (PDAC and other tumors); ≥ Second line | Atezolizumab | Ongoing |
| NCT03080974 | 10 | I | Advanced (stage III) Any line | Nivolumab +Irreversible electroporation | PFS 6.3 m (95%CI: 3.5-10.0); OS 18 m (95%CI: 9.2-26.8) |

OS: Overall survival; PDAC: Pancreatic ductal adenocarcinoma; PFS: Progression-free survival.

A phase I/II clinical trial (NCT02331251) of metastatic PDAC naïve chemotherapy, tested the combination of pembrolizumab (anti-PDL1), nab-paclitaxel and gemcitabine [89], achieving a median PFS and OS of 9.1 and 15.0 mo, respectively[89].

Other combinations such as ipilimumab plus gemcitabine (NCT01473940)[90] or CD40 agonist plus gemcitabine[91] in a phase I clinical trial in first-line treatment have also improved OS in the experimental arm, with an OS of 8.5 mo and 8.4 mo, respectively. CD40 is a member of the tumor necrosis factor receptor superfamily. The binding of CD40 by its ligand or by an agonistic monoclonal antibody activates the receptor and results in APC activation, including DCs, B cells and monocytes. In mouse pancreatic cancer models, the combination of agonistic CD40 monoclonal antibody with gemcitabine plus nab-paclitaxel triggers T-cell-dependent tumor regressions and improves survival benefit, which are further augmented by the addition of an anti-PD-1 monoclonal antibody. The preliminary results from the combination of a CD40 monoclonal antibody agonist combined with gemcitabine plus nab-paclitaxel and PD1 inhibitor have been published, showing a 58% response rate from 24 evaluable patients[92].

The COMBAT/Keynote-2020 clinical trial deserves special mention. This trial is based on CXC chemokine receptor 4 (CXCR4) blockades, that promotes T-cell tumor infiltration and is synergistic with anti-PD-1 therapy in PDAC mouse models. One cohort included 22 patients and combined the CXCR4 antagonist BL-8040 (motixafortide) with pembrolizumab-nanoliposomal irinotecan-fluorouracil-folinic acid in PDAC second-line treatment. The preliminary results showed an objective response rate, disease control rate and median duration of response of 32%, 77% and 7.8 mo, respectively, suggesting that it is indeed a promising strategy in treating PDAC[93].

According to trial results, patients, who received only immunotherapy, experienced 9%-11% of grade ≥ 3 immune related adverse events[76], while patients receiving immunotherapy in combination with chemotherapy presented grade ≥ 3 adverse effects in up to 53%. In these cases the most common toxicities were hematologic[2].

Vaccines treatment as a single agent or in combination

Several types of vaccines have been tested as single agents (Table 3) or in combination with chemotherapy (Table 4) or immunotherapy (Table 5), including whole-cell vaccines, DCs, DNA and peptide vaccines that entail the presentation of immunogenic cancer antigens to the immune system, resulting in the activation of cancer antigen-specific cytotoxic T lymphocytes *in vivo* and the subsequent anticancer immune response[94].

Table 2 Clinical trials on pancreatic ductal adenocarcinoma combining immunotherapy and chemotherapy

| National clinical trial number | Sample | Phase | Settings | Drug | Results |
|---|--------|-------|---|--|---|
| NCT01473940 | 21 | I | Advanced; Metastatic; Any line | Ipilimumab; Gemcitabine | OS 8.5 m (95%CI: 2.2-10.3) |
| NCT00556023 | 34 | I | Metastatic Chemotherapy naïve | Tremelimumab Gemcitabine | OS 7.4 m (95%CI: 5.8-9.4) |
| NCT02331251 | 81 | I/II | Metastatic (PDAC and other tumors) Chemotherapy naïve | Pembrolizumab; Nab-Paclitaxel Gemcitabine | OS 15 m (95%CI: 6.8-22.6) |
| Beatty <i>et al.</i> , <i>Clin Cancer Res</i> 2013; 19 : 6286–6295 | 22 | I | Advanced; First line | CD40 agonist (CP-870893); Gemcitabine | PFS 5.2 m (95%CI: 1.9-7.4); OS 8.4 m (95%CI: 5.3-11.8); 1-y OS 28.6% |
| NCT01413022 | 47 | I | Borderline; Locally advanced Chemotherapy naïve | CCR2 inhibitor (PF-04136309); FOLFIRINOX | Combination arm: 49% OR Chemotherapy arm: 0% OR |
| NCT02268825 | 39 | I | Advanced; Metastatic (gastrointestinal malignancies) ; Any line | Pembrolizumab mFOLFOX | No results posted |
| NCT02309177 | 138 | I | Advanced; Metastatic (PDAC and other tumors); Any treatment naïve | Nivolumab; Nab-Paclitaxel Gemcitabine | No results posted |
| NCT02077881 | 98 | I/II | Metastatic; First line | IDO inhibitor (indoximod); Nab-Paclitaxel; Gemcitabine | No results posted |
| NCT04045730 | 17 | I/II | Metastatic First line | Gemcitabine; Nab-Paclitaxel; Pembrolizumab | PFS 9.1 m (95%CI: 4.9-13.3); OS 15 m (95%CI: 6.8-23) |
| NCT03214250 | 30 | I | Metastatic; First line | Gemcitabine; Nab-Paclitaxel; Nivolumab; CD40 (agonistic monoclonal antibody) APX005M (sotigalimab) | Ongoing |
| NCT02826486 | 80 | II | Metastatic; Any line | BL-8040; Pembrolizumab; Pegylated liposomal Irinotecan + 5FU | Disease Control Rate 34.5%; OS: 3.3 m Patients receiving study drugs as second-line therapy: 7.5 m |

OS: Overall survival; PDAC: Pancreatic ductal adenocarcinoma; PFS: Progression-free survival; OR: Objective response.

GVAX

The mechanism of actions of GVAX vaccines is the stimulation of APC antigen uptake and T-cell priming through PDAC cell modification to express granulocyte-macrophage colony-stimulating factor (GM-CSF)[95].

A number of phase I and II clinical trials have been conducted on localized PDAC. A phase II clinical trial (NCT00084383) with 60 randomized patients evaluated the effectiveness of the GVAX vaccine administrated in two times: 1) after surgery and before 5-fluoracil based chemotherapy and 2) after chemotherapy had finished. The median PFS was 17.3 mo, and the median OS of 24.8 mo[96].

The GVAX vaccine has also been tested in metastatic PDAC. A phase II clinical trial (NCT01417000) in which 93 patients were randomized to the combination of GVAX plus cyclophosphamide with or without CRS-207 reported an OS of 6.1 mo in the experimental arm *vs* 3.9 mo in the control arm[97]. However, a phase IIb clinical trial (NCT02004262) showed no benefit in its primary endpoint of OS[98].

Algenpantucel

Algenpantucel is a whole cell vaccine that works by harnessing a natural robust immune response against pancreatic cancer[99]. The vaccine has been tested in combination with gemcitabine plus 5-Fluoracil chemoradiotherapy in patients with resected PDAC, achieving a 12 mo PFS of 65% and a 12 mo OS of 83% (*vs* 45% and 63% in the control arm, respectively)[99]. This trial is still on-going for patients with borderline and locally advanced PDAC[99].

KIF20A-66 and survivin-2B 80-88 peptides

KIF20A and survivin are two up-regulated HLA-A24-restricted peptides that have been employed as epitopes in vaccines development[100,101]. KIF20A-66 was tested in a phase I/II clinical trial for patients with metastatic HLA-2402-positive PDAC who

Table 3 Clinical trials on pancreatic ductal adenocarcinoma using vaccines

| National clinical trial number | Sample | Phase | Settings | Drug | Results |
|---|--------|-------|---|--|--|
| UMIN000004919 | 31 | I/II | Metastatic ≥ Second line | KIF20A-66 | KIF20A-66 vaccine: OS 4.7 m ± 0.8; Best supportive care: OS 2.7 m ± 1.1 |
| UMIN000000905 | 6 | I | Advanced (gastrointestinal and endocrine malignancies) ; Any line | SVN-2B; IFA; INFα | > 50% of the patients had positive clinical and immunological responses |
| NCT00569387 | 73 | II | Adjuvant treatment | Algenpantucel-L | 12-m OS: 86% |
| Kaufman <i>et al</i> , <i>J Transl Med</i> 2007; 6 : 955–964 | 10 | I | Advanced; Metastatic; Any line | MUC1; HLA-A2; ICAM-1; LFA-3; CM-CSF | antiCEA/MUC-1 positive: OS 15.1 m; antiCEA/MUC-1 negative: OS 3.9 m |
| Lepisto <i>et al</i> , <i>Cancer Ther</i> 2008; 6 : 955–964 | 12 | I/II | Adjuvant treatment | MUC1 peptide-loaded DC vaccine | Four of twelve patients are still alive without disease recurrence |
| NCT01410968 | 12 | I | Advanced; Metastatic; Any line | w/Poly-ICLC peptide-pulsed DC-CIK | OS 7.7 m |
| Gjertsen <i>et al</i> , <i>Int J Cancer</i> 2001; 92 : 441–50 | 48 | I/II | Surgically resected; Advanced; Any line | K-Ras vaccine GM-CSF | Resected: OS 25.6 m (95%CI: 10-39); Unresectable: OS 10.2 m (95%CI: 3-28) |
| Abou-Alfa <i>et al</i> , <i>Am J Clin Oncol</i> 2011; 34 : 321–5 | 24 | I | Adjuvant (KRAS mutant) | Ras-peptide GM-CSF | OS 20.3 (95%CI: 11.6-45.3) |
| Bernhardt <i>et al</i> , <i>Br J Cancer</i> 2006; 95 : 1474–1482 | 48 | I/II | Advanced Treatment naive | GV1001; GM-CSF | Responders: OS 7.2 m (95%CI: 4.8-10.7); Non-responders: OS 2.9 m (95%CI: 1.7-6.30) |
| Shima <i>et al</i> , <i>Cancer Sci</i> 2019; 110 : 2378-2385 | 83 | II | Unresectable ≥ Second line | Survivin 2B peptide (SVN-2B); Interferon-β | SVN-2B + IFNβ: OS 31.2 d (95%CI: 43-460); IFNβ: OS 39 d (95%CI: 13-153) |

CIK: cytokine-induced killer ; DC: dendritic cells; GM-CSF: granulocyte-macrophage colony-stimulating factor; IFN: interferon; m: months; OS: overall survival; PDAC: pancreatic ductal adenocarcinoma; PFS: progression-free survival.

had progressed to first-line gemcitabine chemotherapy (UMIN000004919). The OS was 4.7 mo in the treated arm *vs* 2.7 mo in the best supportive care arm. The PFS was 1.8 mo in the vaccine arm[100].

Survivine-2B (SVN-2B) is an HLA-A24 restricted peptide that has been investigated since 2003 with inconspicuous results. A clinical trial (UMIN000000905) with 6 HLA-A2402-positive patients was conducted, resulting in a clinical y immunogenic response in 50% of patients[101].

Other vaccines targeting KRAS and MUC-1

These vaccines target distinct tumor antigens based on the identification of mutated oncogenes, such as *KRAS*, altered tumor suppressor genes, such as *TP53*, *CDKN2A*, *DPC4*, *BRCA2*, and *ERBB2*, as well as the overexpression of tumor-associated antigens, such as *CEA* and *MUC-1*, in pancreatic carcinoma cells[102]. A phase I clinical trial was conducted using MUC-1 vaccines in advanced PDAC, the results of which confirmed that a specific T-cell immune response was obtained, achieving a significant improvement in OS (15.3 mo *vs* 3.9 mo)[103].

A phase I/II clinical trial was conducted in the adjuvant setting, the results of which revealed that 4 out of 12 patients survived without disease recurrence[104].

Clinical trials using *KRAS* against vaccines have also been developed. There is a phase I/II study that combines mutant RAS peptides and GM-CSF in patients with resected or locally advanced PDAC, with an OS of 25.6 mo and 10.2 mo, respectively [105].

GV1001 is another tested vaccine. A phase I/II trial combining this vaccine with GM-CSF for unresectable PDAC[106], and observed an immune response in 63% of patients, with an OS of 7.2 mo *vs* 2.9 mo in no-immune responders. After these encouraging results, a phase III study for locally advanced PDAC was conducted [107]. However, the combination of GV1001 plus gemcitabine plus capecitabine did not improve OS compared with chemotherapy alone (6.9 mo *vs* 7.9 mo).

Combination of vaccines treatment with immune checkpoints

Preclinical reports have supported the concept of synergy between cancer vaccines and immune checkpoint blockade in non-immunogenic tumors. Based on these results, several clinical trials have been conducted to assess the efficacy of this combination in

Table 4 Clinical trials on pancreatic ductal adenocarcinoma combining vaccines and chemotherapy

| National clinical trial number | Sample | Phase | Settings | Drug | Results |
|---|--------|-------|--|---|--|
| Jaffee <i>et al</i> , <i>J Clin Oncol</i> 2001; 19 : 145–56 | 14 | I | Adjuvant (stage I/II/III) | CVAX, Chemorradiation | Effective anti-tumor immunity |
| NCT00084383 | 60 | II | Adjuvant (stage I/II) | GVAX; 5FU; Chemorradiation | Combination: OS 24.8 m (95%CI: 21.2–31.6); 5FU/Chemorradiation: OS 20.3 m (95%CI: 18–23.9) |
| NCT01417000 | 93 | Ila | Metastatic ≥ Second line | GVAX/Cy CRS-207 | Combination: OS 6.28 m (95%CI: 4.47–9.40); GVAX/Cy: OS 4.07 m (95%CI: 3.32–5.42) |
| NCT02004262 | 303 | Iib | Metastatic ≥ Second line | GVAX/Cy CRS-207 Chemotherapy | Combination: OS 3.7 m (95%CI: 2.9–5.3); CRS-207 alone: OS 5.4 m (95%CI: 4.2–6.4); Chemotherapy: OS 4.6 m (95%CI: 4.2–5.7) |
| UMIN000008082 | 60 | II | Advanced First line | KIF20A; VEGFR1/2; Gemcitabine | OS 9 m HLA matched; OS 10 m HLA unmatched |
| NCT01072981 | 722 | III | Adjuvant treatment | Algenpantucel-L; Gemcitabine-5FU | 1-y DFS 86% algenpantucel-L vs 63% Gemcitabine-5FU; 1-y OS 65% algenpantucel-L vs 45% Gemcitabine-5FU |
| NCT01836432 | 302 | III | Borderline resectable; Locally advanced unresectable; First line | Algenpantucel-L; FOLFIRINOX; Gemcitabine; Nab-Paclitaxel; Capecitabine; 5FU | No results posted |
| NCT01781520 | 47 | I/II | Unresectable locally advanced Metastatic Chemotherapy naïve | DC-CIK Chemotherapy S-1 | DC-CIK+Chemotherapy S-1: OS 7 m; DC-CIK alone: OS 4.2 m; Chemotherapy S-1 alone: OS 4.7 m; Supportive care only: OS 1.73 m |
| Muscarella <i>et al</i> , <i>J Clin Oncol</i> 2012; 30 : e14501-e. | 176 | II | Resected (KRAS mutant) adjuvant | GI-4000 Gemcitabine | GI-4000+Gemcitabine OS 19.8 m; Placebo-gemcitabine: OS 14.8 m |
| Middleton <i>et al</i> , <i>Lancet Oncol</i> 2014; 15 : 829–840 | 1062 | III | Advanced Metastatic Chemotherapy naïve | GV1001 Gemcitabine Capecitabine | Treated group: OS 6.9 m (95%CI: 6.4–7.6); Chemotherapy alone: OS 7.9 m (95% 7.1–8.8) |
| Yanagisawa <i>et al</i> , <i>Anticancer Res</i> 2018; 38 : 2217–2225 | 8 | I | Adjuvant (I, II, III) | WT1-DC Vaccine S-1 Chemotherapy Gemcitabine | No results posted |
| Suzuki <i>et al</i> , <i>Cancer Sci</i> 2017; 108 : 73–80 | 66 | II | Advanced First line | Antiangiogenic cancer vaccines targeting VEGFR1 and VEGFR2 in addition to the KIF20A peptide; Gemcitabine | PFS HLA matched: 4.7 m; PFS HLA unmatched: 5.2 m |

OS: overall survival; PDAC: pancreatic ductal adenocarcinoma; PFS: progression-free survival; Cy: Cyclophosphamide; VEGFR: vascular endothelial growth factor receptor.

PDAC therapy[108].

In clinical trial NCT00836407, 30 patients with previously treated metastatic PDAC were randomized to a high dose of Ipilimumab (10mg/kg) as the single agent or in combination with the GVAX vaccine. Five patients showed stable disease, and an OS of 5.7 mo was achieved in the experimental arm compared with 3.6 mo in the control arm[108].

Other studies that included patients with metastatic PDAC combined with nivolumab and ipilimumab, with or without GVAX and CRS-207, showed enhanced T-cell responses. Studies are currently evaluating the role of immune checkpoint inhibitors in combination with cyclophosphamide/GVAX and CRS-207 vaccines (NCT02243371, NCT02451982), and the results have yet to be published[99].

Pembrolizumab combined with the modified p53-expressing Ankara virus (p53MVA) vaccine has been studied in patients with several malignancies included PDAC, with clinical responses observed in 3 of 11 patients and disease stabilization for 30, 32 and 49 wk[109].

Vaccines were well tolerated. Most common toxicities were grade 1–2 induration/erythema or pain/soreness at the vaccine sites, pyrexia, chills, fatigue and nausea, with < 5% of patients reporting serious adverse events[96,98–99,106]. There were not reported clinical signs of auto-immune disease, abnormal biochemical or

Table 5 Clinical trials on pancreatic ductal adenocarcinoma combining vaccines and immunotherapy

| National clinical trial number | Sample | Phase | Settings | Drug | Results |
|--------------------------------|--------|-------|---|--|--|
| NCT00836407 | 30 | I | Metastatic ≥ Second line | Ipilimumab GVAX | Combination: OS 5.7 m (95%CI: 4.3-14.7); Ipilimumab: OS 3.6 m (95%CI: 2.5-9.2) |
| NCT02243371 | 93 | II | Metastatic ≥ Second line | Nivolumab Cy; GVAX; CRS-207 | No results posted |
| NCT02451982 | 62 | I/II | Neoadjuvant Adjuvant | Nivolumab Cy GVAX Urelumab | No results posted |
| NCT04627246 | 3 | I/II | Adjuvant | DC vaccine loaded with personalized peptides (PEP-DC); Nivolumab SOC | No results posted |
| NCT02432963 | 11 | I | Advanced (solid malignancies) ≥ Second line | Pembrolizumab p53MVA | Clinical responses in three out of eleven patients |

OS: overall survival; Cy: Cyclophosphamide; SOC: Standard of Care Chemotherapy; p53MVA: Modified Vaccinia Virus Ankara Vaccine Expressing p53.

haematological parameters related with the vaccinations[105]. A grade 5 fatal myocarditis was reported with Pembrolizumab combined with the p53MVA vaccine [109].

Adoptive cell transfer

The most clinically important form of adoptive cell transfer therapy is chimeric antigen receptor (CAR) T-cell therapy (Table 6). CAR-T cells can target any extracellular molecular structure recognizable by an antibody, thereby avoiding the MHC restriction. CAR consists of an extracellular domain of a single-chain variable fragment (scFv) of an antibody that recognizes a specific tumor antigen and an intracellular domain that contains the T cell receptor signal transduction sequence[39]. To generate the appropriate cell therapy product for adoptive transfer, T cells are collected from patients *via* leukapheresis, manipulated to target the specific antigen, expanded, and then reinfused[110].

The ideal target antigen is one that is selectively expressed in tumor cells; however, most targets of CAR-T cells are also expressed in normal tissues such as the mesothelin, CD24, carcinoembryonic antigen (CEA) and human epidermal growth factor receptor 2 (HER2), and have been considered as targets in PDAC[110].

Several clinical trials have followed this approach; however, the use of CAR-T cell therapy in PDAC is scarce, and the clinical results are moderate. For example, a phase I study of Her2-specific CAR-T cells (NCT01935843) showed that 5 out of the 11 treated patients achieved stable disease, while 2 patients achieved partial response with a median PFS of 4.8 mo[111].

However, CAR-T cell therapy might trigger a cytokine release syndrome, a severe complication that consists of the release of cytokines that cause several symptoms including fever and hypotension[110].

The most characteristic toxicity associated with CAR-T therapy is the cytokine release syndrome. If the antigen selected for CAR-T cell therapy is expressed on normal tissues, toxicity and autoimmunity might appear[2].

CONCLUSION

The immune response in cancer is a complex process that involves the balance between tumor-promoting innate immune responses and tumor-suppressing adaptive immune responses. In PDAC, immune evasion is an early event during tumorigenesis and is associated with proinflammatory signals, infiltration of immunosuppressive cells (Tregs and MDSCs), and a sophisticated TME where numerous interactions occur between stromal signals, the immune system and tumor cells. As a consequence, PDAC is characterized by low immunogenicity and antigenicity, a critical concept when developing novel immunotherapeutic approaches for treating PDAC.

The emergence of immunotherapy as a new treatment approach for solid tumors has become a revolution in modern oncology. Immune checkpoint inhibitors improve survival in several tumors, such as melanoma, lung cancer, head and neck, and genitourinary. These tumors, known as “hot tumors”, present numerous mutations

Table 6 Clinical trials on pancreatic ductal adenocarcinoma using adoptive cell transfer

| National clinical trial number | Sample | Phase | Settings | Drug | Results |
|--|--------|-------|--|--|--|
| NCT00570713 | 155 | II | Unresectable First-line | MORb-009 Gemcitabine | Combination: OS 6.5 m (95%CI: 4.5-8.10); Placebo plus Gemcitabine: OS 6.9 m (95%CI: 5.4-8.8) |
| NCT01935843 | 10 | I/II | Advanced (PDAC and other tumors Her2-positive) ≥ Second line | Her2-specific CAR-T cells | OS 4.8 m (95%CI: 1.5-8.3) |
| NCT01781520 | 47 | I/II | Advanced; Any line | DC-CIK Chemotherapy S-1 | DC-CIK + Chemotherapy S-1: OS 7 m DC-CIK alone: OS 4.2 m; Chemotherapy S-1 alone: OS 4.7 m; Supportive care only: OS 1.73 m |
| Aoki <i>et al</i> , <i>Cytotherapy</i> 2017; 19 : 473-485 | 48 | I | Adjuvant | Gemcitabine; Autologous γδ; T-cell transfer | PFS 26 m (no statistical difference); OS No statistical difference |
| NCT01959672 | 11 | I/II | Neoadjuvant | Gemcitabine; Leucovorin-Fluorouracil; Oregovomab; Nelfinavir + SBRT | Prematurely closed; PFS 8.6 m; OS 13 m (95%CI: 7-22) |
| NCT00720785 | 40 | I | Metastatic (PDAC and other tumors) ≥ Second line | Irreversible electroporation (IRE); Allogeneic natural killer cell therapy | No results posted |
| NCT04212026 | 67 | I | Metastatic ≥ Second line | Irreversible electroporation; Allogeneic natural killer cell therapy | Stage III PFS 9.1 m (IRE-NK) <i>vs</i> 7.9 m (IRE); Stage III OS 13.6 m (IRE-NK) <i>vs</i> 12.2 m (IRE); Stage IV OS 10.2 m (IRE-NK) <i>vs</i> 9.1 m (IRE) |
| NCT01583686 | 6 | I | Metastatic ≥ Second line | Mesothelin-CART | 2 patients stabilized diseasePFS patient 1: 3.8 mPFS patient 2: 5.4 m |

CAR: chimeric antigen receptor; DC-CIK: dendritic cell-activated cytokine-induced killer cell; IRE: irreversible electroporation; OS: overall survival; NK: natural killer; PFS: progression-free survival; SBRT: stereotactic body radiation therapy.

that create a high number of neoantigens recognized by effector T cells that are released to fight the cancerous cells. However, in the case of PDAC, these results have not been as spectacular as other tumors' due to the intrinsic characteristics of PDAC, which enable it to self-isolate through a complex stroma, thereby evading the immune system.

Immune checkpoint inhibitors as single agents do not provide a benefit in PDAC. However, their combination with chemotherapy may transform PDAC into a "hot tumor" that is more susceptible to immunotherapy. The outcomes in phase I/II clinical trials using this approach are encouraging, with a benefit in OS in several combinations. Cancer vaccines employed as single-agent treatments or combined with classical chemotherapy, chemoradiotherapy or immunotherapy have promising results in the early phases of clinical trials. However, these outcomes have not been confirmed in more advanced studies. Lastly, adoptive cell transfer, specifically the CART-T cell approach, is still in very early phase of development.

Despite advances in treating PDAC, this tumor continues to be associated with extremely poor outcomes and high mortality. Systemic therapies and new strategies therefore need to be developed to improve patient prognoses, which will depend on an ever-increasing understanding of basic immunity and its role in PDAC. The keys to achieving significant changes in the treatment of PDAC include research into safe novel inhibitors (such as immunosuppressive factor, TAMs, MDSCs, and Tregs), increasing the prophylactic efforts in the early stages of carcinogenesis, deepening the understanding of molecular subtyping in PDAC and conducting appropriate patient selection.

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