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Clinical diagnosis and management of pancreatic cancer: Markers, molecular mechanisms, and treatment options

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Abstract

Pancreatic cancer (PC) is the third-leading cause of cancer deaths. The overall 5-year survival rate of PC is 9%, and this rate for metastatic PC is below 3%. However, the PC-induced death cases will increase about 2-fold by 2060. Many factors such as genetic and environmental factors and metabolic diseases can drive PC development and progression. The most common type of PC in the clinic is pancreatic ductal adenocarcinoma, comprising approximately 90% of PC cases. Multiple pathogenic processes including but not limited to inflammation, fibrosis, angiogenesis, epithelial-mesenchymal transition, and proliferation of cancer stem cells are involved in the initiation and progression of PC. Early diagnosis is essential for curable therapy, for which a combined panel of serum markers is very helpful. Although some mono or combined therapies have been approved by the United States Food and Drug Administration for PC treatment, current therapies have not shown promising outcomes. Fortunately, the development of novel immunotherapies, such as oncolytic viruses-mediated treatments and chimeric antigen receptor-T cells, combined with therapies such as neoadjuvant therapy plus surgery, and advanced delivery systems of immunotherapy will improve therapeutic outcomes and combat drug resistance in PC patients. Herein, the pathogenesis, molecular signaling pathways, diagnostic markers, prognosis, and potential treatments in completed, ongoing, and recruiting clinical trials for PC were reviewed.

Key Words: Pancreatic cancer; Pancreatic ductal adenocarcinoma; Molecular mechanisms; Diagnostic and prognostic markers; Treatment; Clinical trials

Core Tip: Pancreatic cancer (PC) is the third-leading cause of cancer deaths. Pancreatic ductal adenocarcinoma is the most common type of PC in the clinic. Multiple pathogenic processes including inflammation, fibrosis, angiogenesis, epithelial-mesenchymal transition, and proliferation of cancer stem cells are involved in PC initiation and progression. Although some therapies have been approved for PC treatment, the overall 5-year survival rate is still very low. A combined panel of serum markers is very helpful for PC diagnosis. New treatments and more clinical trials are required to search for new potent therapeutic agents and to evaluate their efficacy in PC treatment.

INTRODUCTION

Pancreatic cancer (PC) accounts for 7% of all cancer-related deaths[1]. The overall 5-year survival rate of PC is 9%, with only 3% for metastatic PC[2]. However, the number of PC-induced death cases will increase about 2-fold by 2060[3,4]. Many factors are involved in the development of PC[5-7], including genetic mutations, environmental factors, and metabolic diseases such as obesity and diabetes. The most commonly diagnosed PC in the clinic is pancreatic ductal adenocarcinoma (PDAC), which accounts for more than 90% of all PC cases[4]. The rest of the PC cases are pancreatic neuroendocrine neoplasms. Pancreatic neuroendocrine neoplasms originate from precursor cells in the pancreatic ductal epithelium with neuroendocrine differentiation, which can be divided into well-differentiated pancreatic neuroendocrine tumors and poorly differentiated pancreatic neuroendocrine carcinomas[8].

PC is a heterogenous and desmoplastic cancer. Genetic variants of tumor cells, immunosuppressive tumor microenvironment (TME), high metastatic rate, and limited therapeutic outcomes cause challenges for current therapies[9-11]. Early diagnosis of PC is critically important for longer survival outcomes. Serum biomarkers can be applied for PC diagnosis, including microRNAs[12] and cancer antigens such as carbohydrate antigen 19-9 (CA 19-9)[13]. In addition, some of these markers such as CA 19-9 can be applied to predict tumor recurrence and survival of PC patients[14,15].

Herein, this review first summarized the pathogenic factors and their associated molecular signaling pathways that are involved in PC development and progression. Then, diagnostic and prognostic markers were reviewed, especially serum biomarkers. Based on the pathogenic factors, corresponding treatments were discussed, and currently completed, ongoing, and recruiting clinical trials for PC treatment were summarized.

PATHOGENESIS OF PANCREATIC CANCER AND RELATIVE MOLECULAR MECHANISMS

The initiation and progression of PC are impacted by many factors, including chronic inflammation or pancreatitis, fibrosis, immunosuppressive TME, epithelial-mesenchymal transition (EMT), proliferation and differentiation of cancer stem cells, and alteration of gut microbiota. In this section, we discussed each of these factors in PC pathogenesis.

Inflammation

Inflammation is a key mediator for the initiation and progression of PC[16]. In TME during PC development, tumor growth accompanies the infiltration of innate and adaptive immune cells. For example, tumor-associated macrophages are one of the major immune cells in the TME, which have been shown to play an essential role in the initiation, progression, and metastasis of PC as well as chemotherapeutic resistance[17]. Tumor necrosis factor alpha-expressing macrophages are recruited by monocyte chemoattractive protein-1 or CCL2, which can induce the reprogramming of classical neoplastic cells into an aggressive phenotype *via* the bromodomain-containing protein 4-mediated signaling pathway[18]. In addition, other infiltrating immune cells including monocytes, myeloid-derived suppressor cells, natural killer cells, neutrophils, and CD4^{+} and CD8^{+} T cells interplay with cancer cells by secreting cytokines. Molecular signaling pathways such as nuclear factor-κB, reactive oxygen species, and toll-like receptors (TLRs) are involved in the inflammatory condition in the TME of

PC[16].

Both local and systemic inflammation contributes to PC development and progression. A clinical study showed that PDAC patients with systemic inflammation characterized by a neutrophil/lymphocyte ratio > 3.1 have a lower median overall survival compared to patients with a neutrophil/lymphocyte ratio < 3.1 in response to the treatment of anti-CD40 monoclonal antibody in combination with gemcitabine[19]. Obesity can induce systemic inflammation and contribute to cancer progression, including PDAC[20]. The chronic low-grade inflammation in white adipose tissues of obese patients plays an important role in PDAC progression[21]. Some important adipokines such as lipocalin 2, proinflammatory cytokines [*e.g.*, tumor necrosis factor alpha and interleukin (IL)-6], and chemokines (*e.g.*, monocyte chemoattractive protein-1 or CCL2) drive the progression of PDACs[21,22].

Chronic pancreatitis characterized by redness and swelling inflammation in the pancreas can be induced by factors such as heavy alcohol consumption[23], smoking, and gallstones[24]. It is a risk factor for the initiation of the progression of PDAC[25] or PC[26]. In the United States, 1.04% of patients with chronic pancreatitis were diagnosed with PDAC, which was higher than the rate in the control group (0.2%)[27]. Therefore, targeting inflammation is a therapeutic strategy for PC treatments.

Desmoplastic stroma

Chronic pancreatitis and PC are commonly associated with desmoplastic tissue proliferation, which is mainly caused by activated pancreatic stellate cells[28]. Fibrotic stroma is formed by fibroblasts and their secreted extracellular matrix proteins that contribute to cancer cell proliferation and invasion, an immunosuppressive environment, and therapeutic resistance[29]. Some molecules including epithelium-specific E-twenty six factor 3[30], galectin-1[28], β-catenin[31], and transforming growth factor-β1 (TGF-β1)[32] are essential drivers for pancreatic stellate cell activation in PC. In addition, activated pancreatic stellate cells can secrete many molecules, such as IL-6, TGF-β1, stromal cell-derived factor-1, hepatocyte growth factor, and galectin-1, to induce PC cell proliferation, migration, and chemotherapeutic resistance[33].

Cancer-associated stromal fibroblasts (CAFs) are a heterogenous cell population, which can secrete many factors to regulate inflammation, cancer development, progression, metastasis, recurrence, and drug resistance[34]. For instance, CAFs and tumor cells can crosstalk through extracellular vesicles (EVs). Annexin A6-enriched EVs secreted by CAFs can increase the aggressiveness of PDACs[35,36]. CD9 is an important component of these EVs[36]. In addition, the uptake of CD9+ANXA6+ EVs secreted by CAFs can activate the mitogen-activated protein kinase signaling pathway to promote PC cell migration and EMT[36].

Immunosuppressive TME

Overexpression of immune checkpoints, such as programmed cell death protein 1 (PD-1), lymphocyte-activation gene 3, and cytotoxic T-lymphocyte-associated antigen 4, and their ligands programmed death-ligand 1 (PD-L1) and PD-L2, CD80 and CD86 (cytotoxic T-lymphocyte-associated antigen 4), and major histocompatibility complex molecule II or major histocompatibility complex-II (lymphocyte-activation gene 3) mediate the immunosuppression in TME[37]. Therefore, targeting these molecular signaling axes provide novel therapeutic options. For example, PD-L1 is overexpressed by tumor cells and some immunosuppressive cells in PDAC, which can be targeted by PD-1-expressing chimeric antigen receptor (CAR) T cells to mediate anti-tumor activity by PD-1/PD-L1 interaction[38].

Additionally, other proteins, such as fibroblast activation protein, CD73, and inhibitor of DNA binding 1[39], can mediate the immunosuppressive environment in the TME. In a mouse PDAC model, elevated expression of CD73, a cell surface-localized ecto-5′-nucleotidase, is positively associated with the infiltration of myeloid-derived suppressor cells and expression of granulocyte-macrophage colony-stimulating factor, which causes suppression of interferon-gamma production in intratumoral T cells. The CD73-mediated suppressive effect on T cells can be abolished by genetic knockdown in PDAC cells [40]. In human PDAC cells, the elevated expression of CD73 causes cancer cell resistance to gemcitabine by activating the protein kinase B (AKT) signaling pathway[41].

EMT

EMT plays a pivotal role in PC progression and metastasis, which is defined by cell phenotypic transition from an epithelial to a mesenchymal state[42]. Dermokine genes regulate the oncogenesis of PC. Overexpression of dermokine-α can promote PC cell proliferation, EMT, migration, and invasion by regulating the phosphorylation of signal transducer and activator of transcription 3 (STAT3)[43,44]. Methylsterol monooxygenase 1 as a tumor suppressor can inhibit PC progression by suppressing the phosphoinositide 3-kinase-AKT-mammalian target of rapamycin signaling pathway and EMT[45]. EMT of PC stem cells also plays a critical role in PC initiation and progression, which is discussed in the following section.

Angiogenesis

Angiogenesis plays a key role in PC development, progression, and metastasis, which is commonly associated with the activation of proangiogenic and angiogenic molecules. For example, the epidermal

growth factor receptor is overexpressed in PC cells, which is associated with angiogenesis and cancer cell metastasis[46]. A high density of macrovessels, impaired integrity of microvessels, and poorly perfused vessels are the characterizations of vascularization in TME of PC[29]. Many proteins are involved in the angiogenesis of PC, including vascular endothelial growth factor (VEGF), platelet-derived growth factor, fibroblast growth factor, and their receptors such as VEGF receptors (VEGFR1-3) [29]. In inflammatory conditions, the expression of fibroblast growth factor 1 on PC cells is stimulated by inflammatory product prostaglandin E2, resulting in the proliferation of CAFs and an increased VEGFA expression to maintain angiogenesis[47].

Cancer stem cells

Cancer stem cells (CSCs) are a small part of the TME, where they play a vital role in chemotherapy resistance. Pancreatic CSCs express several surface markers such as CD24, CD44, CD133, C-X-C chemokine receptor type 4, tyrosine-protein kinase Met, epithelial cell adhesion molecule, and double-cortin like kinase 1 as well as intracellular markers such as aldehyde dehydrogenase 1 and RNA polymerase II-associated factor 1[48]. One study showed that miR-497 can resensitize pancreatic CSCs to gemcitabine treatment by inhibiting nuclear factor-κB expression[49]. Exosomes can horizontally transfer drug-resistant traits from gemcitabine-resistant pancreatic CSCs to gemcitabine-sensitive PC cells by delivering miR-210[50]. Small nucleolar RNAs such as SNORD35A play an important role in the proliferation, migration, invasion, and EMT of pancreatic CSCs through regulating the hepatocyte growth factor/tyrosine-protein kinase Met signaling pathway, which is a prognostic biomarker and therapeutic target for PC treatment[51]. In addition, CSCs are involved in drug resistance. For instance, a hypoxic niche can further activate AKT/Notch1 signaling pathway to enhance gemcitabine-induced stemness to cause chemoresistance[52].

Alteration of gut microbiota

Gut microbiomes, including bacteria, viruses, archaea, and fungal species, play important roles in energy digestion, synthesis of secondary bile acids, vitamins and proteins, and immune regulation. Most of the microbes reside (> 95%) within the gut and maintain intestinal homeostasis[53]. Dysbiosis of gut microbiota can regulate inflammation and immune response in the TME to promote cancer progression[54,55], including PC[56,57]. A preclinical study showed that gut microbiota can promote PDAC progression by regulating the infiltration and anti-cancer activity of natural killer cells in the TME[58]. Cohort studies in three different countries from Asia (Japan) and Europe (Spanish and German) showed that *Streptococcus* and *Veillonella spp* were significantly enriched and *Faecalibacterium prausnitzii* was depleted in gut microbial profiles of PDAC patients[59]. A comprehensive analysis of microbiota in several tumors including PC showed that most intratumor bacteria were present intracellularly in both cancer and immune cells[60].

Recent studies also showed that intratumor bacteria were associated with the survival time of PDAC patients[61,62]. In addition, bacteria-mediated treatment (*e.g.*, a bacterium *Megasphaera sp. XA511*) can enhance the anti-tumor effect of anti-PD-1 treatment[61]. Another study also revealed that the alpha diversity of tumor microbiota was higher in long-term survival patients compared to that in short-term survival patients. Fecal microbiota transplantation from humans into mice can regulate tumor growth and anti-tumor immune response[62]. Moreover, pancreatic secretions (*e.g.*, antimicrobial peptides) influence the change of gut microbiota profiles, and the pancreas-bacteria interplay forms a gut-microbiota-pancreas axis[63].

Oral microbiota may also impact the development of PC. One study showed that the presence of oral *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* was positively associated with a high PC risk, whereas genus *Leptotrichia* (phylum Fusobacteria) was related to a low PC risk[64]. In addition, other oral bacterial species including *Clostridium difficile*, *Campylobacter jejuni*, *Escherichia coli*, *Enterococcus faecalis*, *Helicobacter pylori*, *Fusobacterium nucleatum*, *Vibrio cholera*, and *Porphyromonas gingivalis* have been reported to be associated with PC development, which may regulate anti-tumor immunity by signaling pathways such as the miR-21/phosphatase and tensin homolog axis[65].

Overall, multiple factors influence the initiation and progression of PC, which is summarized in Figure 1.

DIAGNOSTIC AND PROGNOSTIC MARKERS FOR PANCREATIC CANCER

The tumors in PC patients can be classified into resectable, borderline resectable, locally advanced, and metastatic tumors[66]. Early diagnosis ensures curable treatment by surgical resection[67]. An accurate diagnosis of PC can improve therapeutic outcomes. Although there is an advanced improvement in new diagnostic technologies, biopsy is still the gold standard for PC diagnosis[68]. Imaging methods including computed tomography, positron emission tomography, magnetic resonance imaging, and endoscopic ultrasound are commonly applied in PC diagnosis and staging[68,69]. In addition, several serum markers have promising diagnostic and prognostic values for PC.
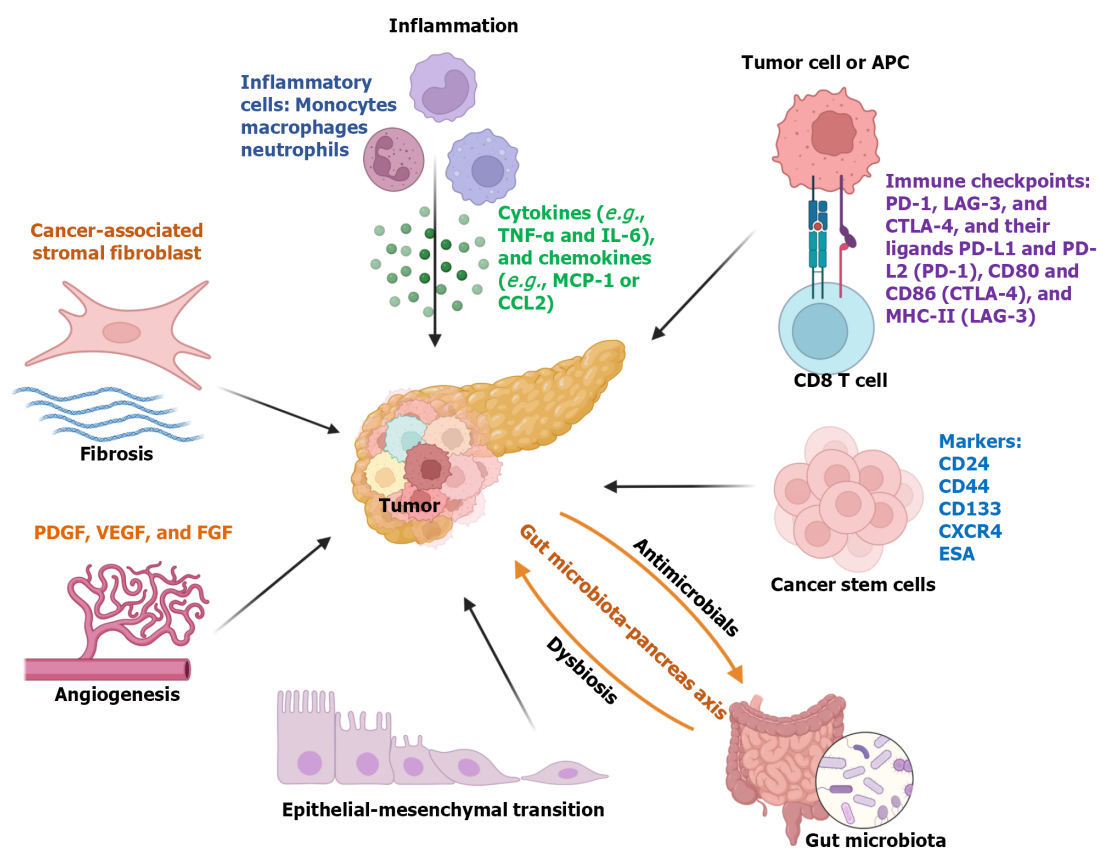
DOI: 10.3748/wjg.v28.i48.6827 **Copyright** ©The Author(s) 2022.

Figure 1 Many factors are involved in pancreatic cancer initiation and progression. Many factors contribute to pancreatic cancer initiation and progression, including inflammation, fibrosis, angiogenesis, dysbiosis of gut microbiota, cancer stem cells, and immune suppressive tumor microenvironment. APC: Antigen-presenting cells; CTLA-4: Cytotoxic T-lymphocyte-associated antigen 4; CXCR: C-X-C chemokine receptor; ESA: Epithelial-specific antigen; FGF: Fibroblast growth factor; IL: Interleukin; LAG-3: Lymphocyte-activation gene 3; MCP-1: Monocyte chemoattractive protein-1; MHC: Major histocompatibility complex; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; PDGF: Platelet-derived growth factor; TNF-α: Tumor necrosis factor alpha; VEGF: Vascular endothelial growth factor. All cartoons in this figure were prepared using Biorender (https://biorender.com).

Serum markers for PC diagnosis

Serum markers including carcinoembryonic antigen and CAs can be applied in PC diagnosis and prognosis[70,71]. Currently, CA 19-9 is the most broadly used serum biomarker for PC diagnosis. A meta-analysis showed that the average sensitivity and specificity of CA 19-9 in PC diagnosis were 72% [95% confidence interval (CI): 71%-73%] and 86% (95%CI: 85%-86%), respectively, with an area under the curve (AUC) of 0.8474 (95%CI: 0.8272-0.8676)[72]. It has been reported that CA 19-9 serum levels are significantly associated with positive lymph nodes and positive margin status in patients with resectable PDAC, which is important for the decision of neoadjuvant treatments[73]. In addition, the preoperative levels of CA 19-9 are negatively associated with the overall survival, nodal involvement, and margin status positivity in resectable PC. However, some limitations impair the role of CA 19-9 in PDAC preoperative staging and management[74], including up to 50% of PDAC patients without CA 19-9 secretion.

In combination with other markers, the diagnostic value of CA 19-9 can be amplified or increased. For example, a combination of CA19-9 with serum mucin 5AC, a heavily glycosylated protein of the mucin family, improves both sensitivity (73.8%) and specificity (88.6%) as well as the AUC (0.894; 95%CI: 0.844-0.943) for PC diagnosis in patients, better than the values of each individual marker[75]. There are many other serum markers that can be used for PC or PDAC diagnosis, including macrophage inhibitory cytokine-1[76], keratin 8[77], protein induced by vitamin K absence II[78], and gremlin 1 (GREM1)[79] (Table 1). Meanwhile, combining different markers in a panel could increase the values of sensitivity, specificity, and AUC. For example, a panel including CA 19-9, factor VIII, fibrinogen, albumin, and alkaline phosphatase increase the AUC value to 0.95 (95%CI: 0.89-0.99) when compared to 0.80 (0.71-0.88) for CA 19-9 alone in distinguishing PDAC from intraductal papillary mucinous neoplasm, a benign tumor[80]. Another study also showed that a panel of four biomarkers including S100 calcium-binding protein A2, S100 calcium-binding protein A4, CA 125, and CA 19-9 increased AUC to 0.913[81].

Table 1 Diagnostic markers of pancreatic cancer

Cancer type	Markers	Expression	Sensitivity	Specificity	AUC	Ref.
PC	CA 19-9	Serum	72.0%	86%.0	0.8474	[72]
PC	MUC5AC + CA19-9	Serum	73.8%	88.6%	0.8940	[75]
PC	MIC-1	Serum	80.0%	85.0%	0.8945	[76]
PDAC	Keratin 8	Serum	80.0%	85.0%	0.8945	[77]
PDAC	PIVKA-II	Serum	78.7%	90.7%	0.9000	[78]
PDAC	GREM1	Serum	Unknown	Unknown	0.7180	[79]

AUC: Area under the curve; CA19-9: Carbohydrate antigen 19-9; GREM1: Gremlin 1; MIC-1: Macrophage inhibitory cytokine-1; MUC5AC: Mucin 5AC; PC: Pancreatic cancer; PDAC: Pancreatic ductal adenocarcinoma; PIVKA-II: Protein induced by vitamin k absence II.

MicroRNAs are small non-coding RNAs with about 22 nucleotides, which regulate the expression of their target mRNAs through degradation or translational repression. Serum expression profiles of microRNAs in PC patients are significantly changed compared to healthy controls. Among them, a panel model including miR-125a-3p, miR-5100, and miR-642b-3p showed the most promising value for PC diagnosis with an AUC of 0.95, sensitivity of 0.98, and specificity of 0.97[82]. Another study also showed that serum microRNAs such as miR-25-3p, miR-19a/b-3p, miR-192-5p, miR-223-3p, and let-7b-5p were upregulated in PC patients and can be used as diagnostic markers as a panel[83].

Multi-omics profiling studies can provide new markers for PC diagnosis. Proteomic analysis of EVs derived from co-cultured epithelial and stromal cells in the condition mimicking TME showed that kinesin family member 5B and secreted frizzled related protein 2 had promising values as early PC biomarkers[84]. PancRISK score evaluated by three urine markers, including lymphatic vessel endothelial hyaluronan receptor 1, regenerating family member 1 beta, and trefoil factor 1, showed reasonable sensitivity and specificity for PDAC detection compared to CA 19-9[85]. Another study also showed that a panel of three urine markers with CA 19-9 had pre-diagnostic values before PDAC diagnosis, with a sensitivity of 72% at 90% specificity up to 1 year and 60% sensitivity with 80% specificity up to 2 years[86].

Bioinformatics analysis showed that gremlin 1, a bone morphogenetic protein signaling regulator, was overexpressed in PDAC and predicted a poorer prognosis for patients with PDAC[79]. In addition, serum gremlin 1 is increased in PDAC patients compared to healthy controls and has a diagnostic value. In combination with CA 19-9, the AUC value increases from 0.718 to 0.914[79].

Prognostic markers of pancreatic cancer

One study displayed that PC patients with low lymphocyte-C-reactive protein ratio have significantly low recurrence-free survival and overall survival values[87]. Another study showed that the systemic immune-inflammation index, which is calculated using the absolute platelet, neutrophil, and lymphocyte counts [systemic immune-inflammation index = platelet × (neutrophil/lymphocyte)], can be used as an independent negative prognostic marker of overall survival of PDAC patients receiving neoadjuvant therapy[88]. A meta-analysis showed that mucin 4 (hazard ratio = 2.04, 95%CI: 1.21-3.45) and mucin 16 (hazard ratio = 2.10, 95%CI: 1.31-3.37) had predictive values for the prognosis of PC patients[89]. The expression of aquaporin-5, a water channel protein, is increased in pancreatic adenocarcinoma (PAAD), which is positively associated with the infiltration of different immune cells (*e.g.*, macrophages) in tumors and poor prognosis of PAAD patients[90]. A bioinformatics study showed that overexpression of matrix metallopeptidase 14 and collagen XII alpha 1 is significantly related to the poor prognosis of PAAD patients[91]. Analysis of RNA sequencing data from the Gene Expression Omnibus and the Cancer Genome Atlas databases gives us some conclusion that some biomarkers such as transmembrane protein 170B (TMEM170B) can be applied to predict cancer progression[92]. Overall, improvement in bioinformatics and new technologies accelerates the development of new diagnostic and prognostic markers for PC, which will result in good outcomes for PC therapy.

TREATMENT OPTIONS

Surgical resection is a curable therapy for patients with early stages of PC and good health conditions [66,68]. There are some Food and Drug Administration (FDA)-approved drugs for PC treatment (Table 2), including belzutifan[93,94], erlotinib hydrochloride[95,96], everolimus[97,98], fluorouracil, also known as 5-fluorouracil[99,100], gemcitabine hydrochloride[101,102], irinotecan hydrochloride liposome[103,104], mitomycin[105,106], olaparib[107,108], paclitaxel albumin-stabilized nanoparticle

Table 2 Food and Drug Administration-approved treatments for pancreatic cancer patients

Drug names	Conditions	Targets	Ref.
Belzutifan	Pancreatic neuroendocrine tumors	An inhibitor of hypoxia-inducible factor-2α	[93, 94]
Erlotinib hydrochloride	Gemcitabine hydrochloride-treated PC, not removable with surgery, with metastasis or local progression	An EGFR inhibitor	[95, 96]
Everolimus	Progressive pancreatic neuroendocrine tumors, not removable with surgery, with metastasis or local advance	A mammalian target of rapamycin inhibitor	[97, 98]
Fluorouracil, also called 5-FU	Pancreatic cancer	An anti-metabolite drug with multiple functions such as inhibition of cellular thymidylate synthase to prevent DNA replication and inhibit RNA synthesis	[99, 100]
Gemcitabine hydrochloride	PC with metastasis, local advance, or fluorouracil treatment	An antimetabolite drug and an inhibitor of DNA synthesis	[101, 102]
Irinotecan hydrochloride liposome	Metastatic PC or gemcitabine hydrochloride-treated PC with precision	An inhibitor of topoisomerase I	[103, 104]
Mitomycin	Pancreatic adenocarcinoma with local advance or metastasis to other parts of the body, which has no approvement with other types of treatment	An inhibitor of DNA synthesis and thioredoxin reductase	[105, 106]
Olaparib	Metastatic PC after first-line therapy with platinum chemotherapy and with certain germline mutations in the breast cancer 1 or BRCA2 gene	A poly ADP-ribose polymerase inhibitor	[107, 108]
Paclitaxel albumin-stabilized nanoparticle formulation	PC with metastasis	It prevents cell mitosis and inhibits the growth of cancer cells	[109, 110]
Sunitinib malate	Progressive neuroendocrine tumors that are not removable with surgery, with metastasis to other parts of the body or local advance	An antiangiogenic tyrosine kinase inhibitor	[111, 112]

EGFR: Epidermal growth factor receptor; PC: Pancreatic cancer.

formulation[109,110], and sunitinib malate[111,112]. In addition, combined treatments including leucovorin calcium (folinic acid) + fluorouracil + irinotecan hydrochloride + oxaliplatin, gemcitabine hydrochloride + cisplatin, gemcitabine hydrochloride + oxaliplatin, and oxaliplatin + fluorouracil + leucovorin calcium (folinic acid) have been also approved by the United States FDA for PC treatment [113-115].

In this section, we discussed some treatments targeting the driving factors of PC, including immune checkpoint inhibitors, antifibrosis, anti-inflammation, anti-angiogenesis, growth factor inhibitors, anti-cancer peptides, alteration of gut microbiota, T cell therapy, and oncolytic viruses as well as combined therapies.

Immune checkpoint inhibitors

Immunotherapy by targeting immune checkpoints such as PD-1 and PD-L1 has achieved big success in the treatment of many different tumors[116,117]. Currently, pembrolizumab (anti-PD-1) is the only FDA-approved immune checkpoint inhibitor for the treatment of patients who have advanced PDACs with mismatch repair deficiency or microsatellite instability high[118]. There are many ongoing clinical trials for the evaluation of synergistic effects of ipilimumab or tremelimumab (anti-cytotoxic T-lymphocyte-associated antigen 4 antibody), nivolumab (anti-PD-1 antibody), and durvalumab (anti-PD-L1 antibody) with other chemotherapy, vaccines, or radiotherapy[119].

Antifibrotic treatments

CAFs are one of the most abundant stromal cells in PDAC and contribute to cancer progression and chemoresistance[120]. Therefore, reshaping the fibrotic stroma is a strategy to treat PC. The integrin-mediated signaling pathway plays a critical role in remodeling and induction of pancreatic tissue stiffness during PC development and progression, promoting chemoresistance. The phosphorylation of tyrosine397 in focal adhesion kinase (FAK) of CAFs is significantly increased compared to that in fibroblasts of the normal pancreas. Therefore, inhibiting FAK activity can dramatically suppress CAF migration and extracellular matrix deposition[120]. Meanwhile, FAK inhibition can also resensitize PDAC cells to chemotherapy[121]. Some tyrosine kinase inhibitors such as cabozantinib, pazopanib, lenvatinib, and surufatinib are under clinical evaluation for the treatment of pancreatic neuroendocrine tumors[122]. A study in a murine PC model also showed that stromal hyaluronan degradation by PEGylated recombinant human hyaluronidase in combination with FAK inhibitor could improve anti-

PD-1 antibody efficacy on the survival of PDAC-bearing mice by increasing T cell infiltration and efficacy[123].

Anti-inflammatory treatments

The anti-inflammatory drug aspirin can inhibit cell proliferation of PC cell lines by suppressing cyclin D1 expression to induce G_0/G_1 cell cycle arrest. Aspirin can also inactivate the glycogen synthase kinase-3β signaling pathway and regulate the expression of microRNAs in PC cells[124]. A phase I trial (https://clinicaltrials.gov, registration number NCT03207724) showed that treatment with bermekimab (anti-IL-1α antibody) can decrease inflammatory cytokines and endothelial growth factor, which is associated with an increase in healthy gut microbiota *Akkermansia* compared to the baseline[125]. A phase 3 clinical trial (NCT02923921) showed that adding pegilodecakin (PEG, a pegylated recombinant human IL-10) to folinic acid, fluorouracil, and oxaliplatin increased the expression of total IL-18, interferon-gamma, and granzyme B and decreased TGF-β in patients with post-gemcitabine metastatic PDACs[126].

Anti-angiogenesis treatments

The expression of mitofusin-2 in PC tissues is significantly decreased, which is negatively associated with VEGFA expression. A molecular study showed that overexpression of mitofusin-2 could inhibit the expression of VEGFA, VEGFR2, angiopoietin-1 gene, and tissue inhibitor of metalloproteinase 1 in human umbilical vein endothelial cells[127]. Another study showed that escin, a pentacyclic triterpenoid isolated from the horse chestnut, can inhibit angiogenesis by suppressing the expression of IL-8 and VEGF in PC cells through the blockade of nuclear factor-κB[128]. Treatment with apatinib, a small molecule targeting VEGFR2, can inhibit the proliferation, migration, and invasion of PC cells (ASPC-1 and PANC-1 cells) and the growth of their xenografted tumors by inhibiting cancer cell growth and angiogenesis *via* suppression of the phosphorylation of VEGFR2, AKT, and ERK1/2[129].

Anti-growth factors and growth factor receptor inhibitors

Growth factors play essential roles in PC cell survival, progression, and drug resistance[130]. For example, TGF-β contributes to PDAC progression by inducing N-glycomic changes in SMA-related and MAD-related protein 4-deficient PDAC cell line PaTu-8955S cells[131].

Anti-cancer peptides

Anti-cancer peptides are short peptides with direct and indirect anti-cancer properties. Anti-cancer peptides can be classified into natural and synthetic peptides. For example, human cathelicidin peptide LL-37 can suppress PC growth *in vitro* and *in vivo* by activating the mammalian target of rapamycin signaling pathway to suppress autophagy of PC cells and induce reactive oxygen species production to cause DNA damage and cell cycle arrest[132]. KS-58, a derivative of KRpep-2d that is an artificial cyclic peptide that can selectively inhibit K-Ras (G12D), can suppress the human PC cell line PANC-1 proliferation *in vitro*. In addition, KS-58 also displays anti-tumor activity in subcutaneous and orthotropic PANC-1 cell xenografted tumors, which shows a synergistic effect with gemcitabine[133].

Alteration of gut microbiome

Patients with high levels of antibodies against a pathogenic periodontal bacterium *Porphyomonas gigivalis* have a double risk of developing PC compared to subjects with low levels of antibodies. In contrast, individuals who have high levels of antibodies against commensal oral bacteria reduce the risk of PC development[134]. The microbiome in the cancerous pancreas can induce immune tolerance by causing macrophage-mediated suppression of T cell functions through TLR signaling pathways (*e.g.*, TLR2 and TLR5)[135]. Depletion of gut microbiota by antibiotics can inhibit tumor progression and metastasis *via* upregulation of interferon-gamma-producing T cells and downregulation of IL-10 and IL-17A-producing T cells[136]. Therefore, the alteration of microbial components in the gut and mouth, as well as the TME, can effectively inhibit PC progression.

CAR-engineered T cell therapy

CAR-engineered T cell (CAR-T) therapy shows potential for many tumors. To date, six CAR-T products have been approved by the United States FDA for the treatment of hematopoietic cancers, such as B-cell acute lymphoblastic leukemia (tisagenlecleucel), mantle cell lymphoma (brexucabtagene autoleucel), and multiple myeloma (idecabtagene vicleucel)[137]. However, current clinical trials of CAR-T therapy in PC patients have not shown significance in the improvement of survival and other outcomes[138]. CAF-derived extracellular matrix proteins, enzymes, and growth factors impact the infiltration and efficacy of CAR-T. Enhancing the expression of chemokine ligands such as chemokine (C-C motif) ligand 19 (CCL19) can increase the infiltration of the CAR-T to promote their anti-PDAC efficacy[139].

Oncolytic viruses

Virus-mediated delivery of cytokines and shRNAs shows promising effects in PC treatment. Oncolytic viruses are designed to directly target tumor cells or to activate anti-tumor immune responses.

However, treatment of oncolytic viruses alone is not sufficient to eliminate PC to date[140]. For example, oncolytic adenoviruses loading CD55-ST13 (suppression of tumorigenicity 13)-tumor necrosis factor-related apoptosis-inducing ligand can significantly inhibit but not delete tumor development in a murine xenografted PDAC tumor model by inducing cancer cell apoptosis[141].

Combined therapies

The combined therapy of MEK inhibitor (trametinib) and STAT3 inhibitor (ruxolitinib) inhibits the phenotype of proinflammatory and myofibroblastic IL6+CXCL1+LRRC15+CAFs and increases mesenchymal stem cell-like Ly6a+Cd34+CAFs in a murine model detected by single-cell RNA sequencing[142]. The CAF phenotype change is associated with M2-to-M1 reprogramming of tumor-associated macrophages s and effector CD8+ T cell infiltration. In addition, treatment of MEK and STAT3 inhibitors together with a PD-1 inhibitor (nivolumab) shows clinical benefit in patients with chemotherapy-refractory metastatic PDACs[142]. In contrast, a pharmacodynamic separation treatment for erlotinib plus gemcitabine can improve their treatment efficacy, especially for patients with detected plasma Kirsten rat sarcoma virus mutation[143].

Four-week intraperitoneal injection of gemcitabine together with oral administration of probiotic cocktails (*Lactobacillus paracasei* GMNL-133 and *Lactobacillus reuteri* GMNL-89) can inhibit pancreatic intraepithelial neoplasia formation and suppress serum levels of aspartate aminotransferase and alanine aminotransferase and the expression of vimentin and Ki-67 in pancreatic sections[144].

CLINICAL TRIALS

Some treatments are under clinical investigation, see Table 3 (https://clinicaltrials.gov, accessed on September 6, 2022). These treatments include galunisertib plus gemcitabine[145], Janus kinase 1/2 inhibitor ruxolitinib[146], adoptive transfer of T cells[147], gemcitabine and trastuzumab plus erlotinib [148], erlotinib plus gemcitabine[149], pegilodecakin plus folinic acid, fluorouracil, and oxaliplatin[126], liposomal irinotecan plus 5-fluorouracil/leucovorin[150], bevacizumab[151], and sunitinib[152].

In addition, more than 900 studies in the world are recruiting or enrolling by invitation, and some have a 'not yet recruiting' status for evaluating PC treatments (https://clinicaltrials.gov, accessed on September 17, 2022). A graphic map shows the number of studies at different locations (Figure 2), and some examples are listed in Table 4.

FUTURE PERSPECTIVES

A synergistic treatment is a good option for killing drug-resistant PC cells. For example, astaxanthin can resensitize human PC cells to gemcitabine by activating the hypoxia-inducible factor 1α/STAT3 signaling pathway to promote gemcitabine-induced cell apoptosis and inhibit gemcitabine-induced EMT of PC cells[153]. Guadecitabine, an effective inhibitor of DNA methyltransferase 1, has the potential to resensitize PDAC cells to chemotherapy and immune checkpoint blockade therapy (*e.g.*, anti-PD-L1)[154,155].
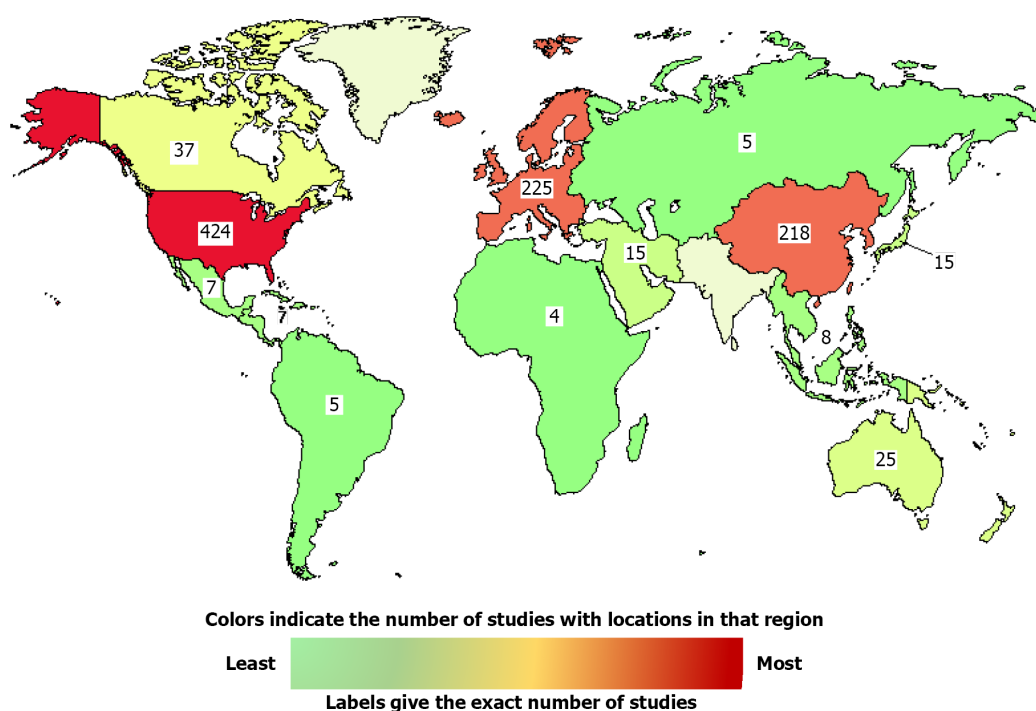
Neoadjuvant therapy has been applied in clinical trials for patients with resectable PDACs, which include neoadjuvant chemotherapy, neoadjuvant radiotherapy, and neoadjuvant chemoradiotherapy [156]. The results from three randomized controlled trials with a total of 130 patients (56 receiving neoadjuvant therapy and 74 in the control group) indicated that neoadjuvant therapy (chemotherapy or chemoradiation + surgery followed by adjuvant therapy) increased the disease-free survival time compared to upfront surgery followed by adjuvant therapy[157]. Another single-center long-term study also showed that PDAC patients with treatment of neoadjuvant therapy, consisting of folinic acid + fluorouracil + irinotecan + oxaliplatin, single gemcitabine, or combined with cisplatin, nab-paclitaxel, or capecitabine with or without radiation had longer median disease-specific survival and disease-free survival than those receiving treatment with upfront surgery[158]. The benefit of neoadjuvant therapy could be a stage-dependent manner. A retrospective cohort study showed that neoadjuvant therapy was positively associated with an improved survival benefit compared with conventional upfront surgery, especially in clinical stage III PC after propensity score matching within each stage[159]. Overall, it can benefit surgical treatment.

Delivery systems can be applied to enhance the efficacy of anti-cancer treatments. For example, arginine glycine peptide-human serum albumin-mediated drug nanoparticles show tumor-targeting effects and increase the cytotoxicity of gemcitabine and curcumin[160]. Administration of VG161, the first recombinant oncolytic herpes simplex virus type 1 that delivers multiple synergistic antitumor immunomodulatory factors, can systematically activate both innate and adaptive immunity and improve the anti-tumor function of the tumor immune microenvironment[161]. Another study showed that using gold nanoparticles could enhance the intracellular delivery of oncolytic adenoviruses into PC cell lines[162]. Radiofrequency hyperthermia also can enhance the local delivery of oncolytic immuno-

Table 3 Completed clinical trials with results for pancreatic cancer treatment

Trial number	Phase	Treatment	Condition
NCT01373164	1b/2	Galunisertib, a TGF-β receptor inhibitor, or placebo plus gemcitabine	Unresectable PC
NCT01423604	2	Ruxolitinib, a Janus kinase 1/2 inhibitor or placebo plus capecitabine	PC
NCT00965718	2	Activated T lymphocyte (*ex vivo*-expanded, CIK cells cultured with anti-CD3 monoclonal antibody and IL-2)	PC
NCT01204372	2	Gemcitabine, trastuzumab plus erlotinib	Metastatic PC
CONKO-005	3	Erlotinib (inhibits the intracellular phosphorylation of tyrosine kinase associated with the EGFR) or placebo plus gemcitabine	Primarily resectable PDAC after R0 resection
NCT02923921	3	Pegilodecakin (a pegylated recombinant human IL-10) plus folinic acid, fluorouracil, and oxaliplatin	Metastatic PDAC
NCT01494506	3	Liposomal irinotecan (it prevents the religation of the DNA strand by binding to the topoisomerase I-DNA complex.) or placebo plus 5-FU/LV	Metastatic PC
NCT01214720	3	Bevacizumab that acts by selectively binding circulating VEGF, thereby inhibiting the binding of VEGF to its cell surface receptors plus chemotherapy	Metastatic PC
NCT00428597	3	Sunitinib, an inhibitor of multiple receptor tyrosine kinases	Metastatic pancreatic neuroendocrine tumors
NCT01525550	4		

5-FU/LV: 5-Fluorouracil/leucovorin; CIK: Cytokine-induced killer; EGFR: Epidermal growth factor receptor; IL: Interleukin; PC: Pancreatic cancer; PDAC: Pancreatic ductal adenocarcinoma; TGF-β: Transforming growth factor beta; VEGF: Vascular endothelial growth factor.

Colors indicate the number of studies with locations in that region

Least — Most

Labels give the exact number of studies

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Figure 2 Recruiting studies for pancreatic cancer at different locations in the world. The studies are in Africa (4), South America (5), Europe (225), the Middle East (15), the United States (424), Canada (37), Mexico (7), Pacifica (25), Japan (15), East Asia (218), North Asia (5), and Southeast Asia (8).

virotherapy for PAAD *in vitro* and *in vivo*[163].

Furthermore, radiofrequency ablation may be applied to treat patients with PC who are unfit for surgery and includes endoscopic ultrasound-guided radiofrequency ablation[164] and endoluminal biliary radiofrequency ablation[165].

Table 4 Ongoing or recruiting clinical trials for pancreatic cancer treatment

Trial number	Phase	Treatments	Conditions
NCT03192462	1 or 2	Intravenous infusions of TAA-specific cytotoxic T lymphocytes	Pancreas cancer with metastatic, locally advanced unresectable, or resectable disease
NCT04637698	1 or 2	Oncolytic viral therapy (Type 2 Herpes simplex virus) expressing GM-CSF	Pancreatic cancer
NCT04247165	1 or 2	Dual checkpoint inhibition (nivolumab and ipilimumab) in combination with gemcitabine and nab-paclitaxel followed by immune-chemoradiation	Borderline resectable, locally advanced, or metastatic pancreatic cancer
NCT05141149	1 or 2	Anti-PAUF monoclonal antibody PBP1510 or in combination with gemcitabine	Advanced/metastatic pancreatic cancer
NCT04825288	1 or 2	Anti-IL-1α true human antibody XB2001 or in combination with ONIVYDE + leucovorin + 5-FU chemotherapy	Advanced pancreatic cancer
NCT03662412	1 or 2	Sirolimus, a selective inhibitor of mTOR	Advanced pancreatic cancer
NCT05131776	2 or 3	Concurrent EUS-guided intratumor injection of P-32 microparticles (OncoSil)	Locally advanced pancreatic carcinoma
NCT03941093	3	Neoadjuvant treatment with pamrevlumab or placebo in combination with either gemcitabine plus nab-paclitaxel or FOLFIRINOX	Locally advanced pancreatic cancer
NCT05529940	3	FOLFIRINOX	Resectable pancreatic cancer
NCT04969731	3	Adjuvant Immuncell-LC (Cytokine-induced killer cells) therapy combined with gemcitabine	Resectable pancreatic cancer
NCT04025840	4	Perioperative epidural block and/or dexamethasone	Resectable pancreatic cancer
NCT04217096	4	Paclitaxel liposome plus S-1, an oral anticancer drug that consists of tegafur, gimeracil, and potassium oteracil in a molar ratio of 1.0:0.4:1.0	Advanced metastatic pancreatic cancer as the first-line therapy

5-FU: 5-Fluorouracil; EUS; Endoscopic ultrasound; FOLFIRINOX: Folinic acid + fluorouracil + irinotecan + oxaliplatin; IL: Interleukin; GM-CSF: Granulocyte macrophage colony-stimulating factor; mTOR: Mammalian target of rapamycin; PAUF: Pancreatic adenocarcinoma up-regulated factor; TAA: Tumor-associated antigen.

CONCLUSION

PDAC is the most common type of PC in the clinic. Multiple factors induce PC development and progression, including but not limited to inflammation, fibrosis, angiogenesis, EMT, and proliferation of CSCs. A combined panel of serum markers is very helpful for PC diagnosis, which is essential for curable therapy. Although several mono or combined therapies have been approved by the FDA for PC treatment, the overall 5-year survival rate is still not promising. The development of novel immuno-therapies such as oncolytic viruses-mediated treatments and CAR-T, combined therapies (neoadjuvant therapy plus surgery), and advanced delivery systems of immunotherapy will improve therapeutic outcomes and combat drug resistance in PC patients. More clinical trials are required to evaluate the efficacy of existing treatments and to find new potent therapies.

FOOTNOTES

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