

World Journal of *Gastrointestinal Oncology*

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The primary aim of *World Journal of Gastrointestinal Oncology* (WJGO, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

INDEXING/ABSTRACTING

The WJGO is now abstracted and indexed in PubMed, PubMed Central, Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 edition of Journal Citation Reports® cites the 2022 impact factor (IF) for WJGO as 3.0; IF without journal self cites: 2.9; 5-year IF: 3.0; Journal Citation Indicator: 0.49; Ranking: 157 among 241 journals in oncology; Quartile category: Q3; Ranking: 58 among 93 journals in gastroenterology and hepatology; and Quartile category: Q3. The WJGO's CiteScore for 2022 is 4.1 and Scopus CiteScore rank 2022: Gastroenterology is 71/149; Oncology is 197/366.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Xiang-Di Zhang; Production Department Director: Xiang Li; Editorial Office Director: Jia-Ru Fan.

NAME OF JOURNAL

World Journal of Gastrointestinal Oncology

ISSN

ISSN 1948-5204 (online)

LAUNCH DATE

February 15, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Monjur Ahmed, Florin Burada

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5204/editorialboard.htm>

PUBLICATION DATE

October 15, 2023

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Systemic treatment for advanced pancreatic cancer

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Wang GX, China; Zhang C, China

Received: July 11, 2023

Peer-review started: July 11, 2023

First decision: August 15, 2023

Revised: August 24, 2023

Accepted: September 22, 2023

Article in press: September 22, 2023

Published online: October 15, 2023



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Abstract

Pancreatic cancer is a deadly disease with an extremely poor 5-year survival rate due to treatment resistance and late-stage detection. Despite numerous years of research and pharmaceutical development, these figures have not changed. Treatment options for advanced pancreatic cancer are still limited. This illness is typically detected at a late stage, making curative surgical resection impossible. Chemotherapy is the most commonly utilized technique for treating advanced pancreatic cancer but has poor efficacy. Targeted therapy and immunotherapy have made significant progress in many other cancer types and have been proven to have extremely promising possibilities; these therapies also hold promise for pancreatic cancer. There is an urgent need for research into targeted treatment, immunotherapy, and cancer vaccines. In this review, we emphasize the foundational findings that have fueled the therapeutic strategy for advanced pancreatic cancer. We also address current advancements in targeted therapy, immunotherapy, and cancer vaccines, all of which continue to improve the clinical outcome of advanced pancreatic cancer. We believe that clinical translation of these novel treatments will improve the low survival rate of this deadly disease.

Key Words: Systemic treatment; Advanced pancreatic cancer; Personalized medicine; Biomarkers; Chemotherapy; Targeted therapy; Immunotherapy

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Core Tip: Understanding the pathophysiology of pancreatic cancer and using personalized treatments might improve patients' overall survival. We think that targeted treatment, immunotherapy, and cancer vaccines can improve the prognosis of patients with advanced pancreatic cancer. As a result, additional study is required to identify the best combination of current drugs to help in early treatment and result in a better clinical outcome.

Citation: Leowattana W, Leowattana P, Leowattana T. Systemic treatment for advanced pancreatic cancer. *World J Gastrointest Oncol* 2023; 15(10): 1691-1705

URL: <https://www.wjgnet.com/1948-5204/full/v15/i10/1691.htm>

DOI: <https://dx.doi.org/10.4251/wjgo.v15.i10.1691>

INTRODUCTION

It is expected that pancreatic cancer will continue to be the leading cause of cancer-related mortality despite a sharp rise in occurrence over the previous several decades. Many of the observed trends are explained by changes in the identified modifiable risk variables as well as changes in the age structure of the global population, particularly in emerging nations. The chance of developing pancreatic cancer is significantly influenced by genetic factors and modifiable exposures, either acting alone or in concert. In order to limit exposures and identify people most at risk of developing this commonly deadly cancer, preventive initiatives, especially primary prevention techniques, will benefit from an understanding of the underlying risk factors and how they interact. Pancreatic cancer detection rates and the precursor lesions that precede it are increasing. This strategy will assist in lowering the rising prevalence of this deadly disease[1-3]. An overview of the knowledge of known risk factors for pancreatic cancer is given in this review, including inherited genetic risk, lifestyle risk, and risk unique to the disease. In addition, we intend to summarize the most recent guidelines for the systemic treatment of pancreatic cancer. We present the data supporting the recommendations that are currently available, with an emphasis on first-line and second-line situations, based on a thorough evaluation of biomedical and clinical trial databases. Finally, we seek the present state of the art and research paths that can enhance targeted treatment and immunotherapy choices for this high-risk patient population.

EPIDEMIOLOGY AND RISK FACTORS

The frequency of pancreatic cancer diagnoses annually has doubled during the previous two decades. Compared to 196000 cases in 1990, there were 441000 cases of pancreatic cancer in the world in 2017. Given that the risk of developing pancreatic cancer rises with age and that it is uncommon to develop the disease before the age of 40, improved diagnosis techniques and the changing age structure of the global population account for the majority of the rise in pancreatic cancer incidence, especially in high-income countries. Incidence rates in low-income nations have remained low due to limited access to contemporary imaging and a lack of pathology expertise, and there is a dearth of high-quality data on mortality in these regions[4,5]. Obesity, type 2 diabetes, and smoking cigarettes are all modifiable risk factors for the development of pancreatic cancer. A significant National Institutes of Health cohort study found that individuals with a body mass index (BMI) outside the normal range had a higher risk of acquiring this malignancy than those with a BMI within the range, with hazard ratios ranging from 1.15 to 1.53. Pancreatic intraepithelial neoplasia, which is a precursor to pancreatic cancer, has been linked to fatty infiltration of the pancreas. There is a long-standing association between diabetes and the development of pancreatic cancer, with a relative risk (RR) of 2.1, even though cancer of the pancreas is also a risk factor for diabetes development[6-9]. One percent of those with newly diagnosed diabetes over the age of 50 experience diabetes as a result of concurrent pancreatic cancer. Similar to this, those who have had their diabetes diagnosis for less than one year have a greater RR of developing pancreatic cancer of 5.4-fold than those who have had it for a long time, who only have a 1.5-fold higher risk. These findings imply that newly diagnosed diabetes may be a significant risk factor and a sign of pancreatic cancer. Pancreatic cancer is thought to be around twice as common among smokers as in non-smokers, according to estimates; however, unlike other smoking-related malignancies, pancreatic cancer does not yet have a well-defined genetic signature[10,11].

On average, genetic risk factors are thought to be responsible for 5%-10% of all pancreatic malignancies. There are several family cancer syndromes that have been linked to a higher chance of getting pancreatic cancer. A mutation in the tumor suppressor STK11 causes Peutz-Jeghers syndrome, which raises the risk of pancreatic cancer by 35%. The chance of acquiring this kind of cancer is further enhanced by the hereditary breast-ovarian cancer syndrome, which is typically linked to mutations in BRCA1 or BRCA2. Despite the fact that people with a BRCA1 mutation have a relatively low chance of developing the disease—a RR of 2.8 compared with 1.3 in the general population—mutations of BRCA2 are a more common genetic risk factor (RR = 3.5) for pancreatic cancer development[12,13]. An elevated risk of pancreatic cancer of 17% has been attributed to inherited mutations in the *CDKN2A* gene. An elevated risk of acquiring this kind of cancer is also linked to germline abnormalities in genes necessary for DNA damage response and DNA repair. Patients with Lynch syndrome are more likely than the general population to acquire pancreatic cancer by the time that they are 70 years old, and their tumors show microsatellite instability, making them particularly susceptible to immune checkpoint inhibitor treatment. Patients with hereditary pancreatitis syndromes, which are linked to mutations in *SPINK1*

and *PRSS1*, have a 40% lifetime chance of getting pancreatic cancer as a result of chronic pancreatitis[14,15].

CLINICAL PRESENTATION

Only a small percentage of patients with pancreatic cancer initially have the illness that can be surgically removed, which is consistent with the fact that pancreatic cancer often causes minimal symptoms prior to progression to the advanced stage. Tragically, individuals who do experience symptoms frequently have vague complaints, such as nausea, bloating, stomach fullness, or changes in stool consistency, which are frequently appropriately ascribed to other benign causes and delay diagnosis and treatment. At the time of diagnosis, stomach discomfort, abnormal liver function tests, jaundice, newly diagnosed diabetes, nausea, vomiting, dyspepsia, weight loss, and back pain are the clinical symptoms that occur most often[16,17]. Approximately 60%-70% of pancreatic tumors are discovered near the head or neck of the organ, and they are more likely to result in biliary blockage and a patient with an identifiable jaundice-free appearance. The range of jaundice's positive predictive value for detecting pancreatic cancer is 4%-13%. Pancreatic body tumors frequently infiltrate nearby vascular systems, such as the portal vein, hepatic, and superior mesenteric veins, and are therefore more likely to manifest with back discomfort. Because they have fewer anatomical neighbors, pancreatic tail tumors frequently have room to develop unchecked and are typically advanced when discovered (Figure 1)[18,19].

ADVANCED PANCREATIC CANCER

TNM staging and clinical categorization, the two separate staging methods, both have prognostic consequences that are helpful for therapeutic suggestions. Patients with borderline resectable and locally advanced pancreatic cancer are grouped together in stage III of the TNM staging system. Most patients with stage I and stage II cancer will fall into the resectable category, although there are a few people with pancreatic cancer that is borderline resectable who may be categorized as stage II, especially when the superior mesenteric or portal vein is involved. As a result, clinical categorization is more beneficial when choosing a course of treatment. Pancreatic cancer is considered advanced when it is unresectable or cannot be removed surgically. The cancer has spread to neighboring lymph nodes or blood vessels, as well as to organs outside the pancreas. Typically, this is stage III or IV. The majority of pancreatic cancer patients are diagnosed with advanced disease. Patients who are detected at an earlier stage of the disease may acquire advanced cancer if it spreads[20].

ADVANCED PANCREATIC CANCER TREATMENTS

Chemotherapy

More than 33% of pancreatic cancer patients have locally progressive disease at the time of diagnosis, frequently as a result of severe vascular involvement that makes surgical resection impossible. The majority of these individuals have incurable illnesses, while a small percentage who have had a great response to treatment could qualify for surgical excision. This patient group is usually given systemic chemotherapy utilizing protocols that have been authorized for use in the context of metastatic disease. Due to a phase 3 trial that demonstrated gemcitabine's therapeutic advantage over fluorouracil, it has been the standard of care for metastatic pancreatic cancer for many years. However, the median survival time was only 5.6 mo, and the response rate (RR) was only 5%[21]. Since then, several trials have been conducted with gemcitabine serving as the main component of doublet or triplet regimens to enhance patients' overall outcomes. The majority of the trials' results were unsatisfactory, with the exception of one that used erlotinib and gemcitabine together. Gemcitabine with erlotinib resulted in a median survival of 6.2 mo in this randomized phase 3 study, as opposed to 5.9 mo in the gemcitabine-only group. Although the difference in 2-wk survival was statistically significant, the increased toxic effects may prevent it from being clinically important[22]. In 2011, Conroy *et al*[23] conducted a randomized control trial to compare the efficacy and safety of "Folinic acid, fluorouracil, irinotecan, and oxaliplatin" (FOLFIRINOX) with gemcitabine in the first-line treatment of 342 advanced pancreatic cancer patients. The trial lasted 6 mo. In the FOLFIRINOX group, the median overall survival (OS) was 11.1 mo, whereas in the gemcitabine group, it was 6.8 mo. The median progression-free survival (PFS) for the FOLFIRINOX group was 6.4 mo as opposed to 3.3 mo for the gemcitabine group. In comparison to the gemcitabine group, which had a 9.4% objective RR (ORR), the FOLFIRINOX group's ORR was 31.6%. More adverse events were recorded in the FOLFIRINOX group, and 5.4% of the patients in this group experienced febrile neutropenia. In contrast to gemcitabine-treated patients, 31% of FOLFIRINOX-treated patients had a significant deterioration in quality of life at 6 mo. They determined that, as compared to gemcitabine, FOLFIRINOX had a survival benefit but increased toxicity. FOLFIRINOX is a therapy option for people with metastatic pancreatic cancer who have a good performance status. Von Hoff *et al*[24] conducted a phase 3 study in 861 patients with metastatic pancreatic cancer to compare the effectiveness and safety of a combination regimen (nab-paclitaxel-gemcitabine) with gemcitabine alone in 2013. They found that the median OS was 8.5 mo in the nab-paclitaxel-gemcitabine combination group and 6.7 mo in the gemcitabine alone group. The nab-paclitaxel-gemcitabine group had a survival rate of 35% at one year compared to 22% in the gemcitabine alone group and 9% compared to 4% at two years. In comparison to the gemcitabine alone group, which had a median PFS of 3.7 mo, the nab-paclitaxel-gemcitabine group's PFS was 5.5 mo. They observed that gemcitabine combined with nab-paclitaxel importantly improved RR, OS, and PFS in patients with

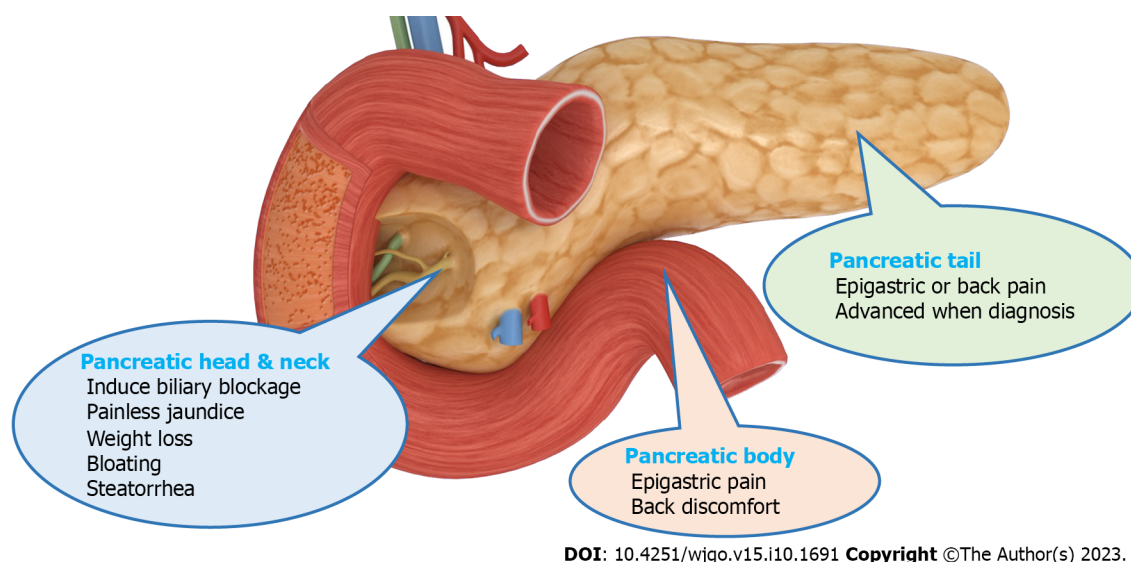


Figure 1 The location of a tumor within the pancreas affects a patient's presentation.

advanced pancreatic cancer but elevated rates of peripheral neuropathy and myelosuppression. Systemic chemotherapy such as FOLFIRINOX or gemcitabine plus nab-paclitaxel continues to be the principal treatment option for patients who have distant metastases at the time of their diagnosis, with the goals of relieving cancer-related symptoms and extending life. Even though first-line gemcitabine plus nab-paclitaxel and FOLFIRINOX have never been directly compared in a randomized controlled trial, real-world retrospective studies reveal that younger and physically fit participants are more likely to be treated with FOLFIRINOX, which results in a better OS in comparison with gemcitabine combined with nab-paclitaxel. Patients whose performance status or comorbidities prevent combination treatment still have the option of gemcitabine monotherapy[25,26]. If a patient's condition allows for chemotherapy and they have advanced on the first-line treatment with FOLFIRINOX, gemcitabine-based chemotherapy is a suitable second-line therapy[27-29].

Targeted therapy

Conventional therapies are treatments that target multiple biological processes; they are unable to distinguish between oncogenic and normal cells, resulting in unfavorable side effects. As a result, tailored therapies using small molecule inhibitors (SMIs) and monoclonal antibodies (mAbs) are required. These drugs work by targeting tumor cell surface receptors, growth factors, or other proteins that are important in disease development and progression. Targeted treatment refers to medications that suppress tumor cell proliferation by interacting with essential molecules in the cells required for cancer development rather than just interfering with rapidly proliferating cells, as typical chemotherapy does. Many researchers are interested in targeted cancer therapy since it is likely to replace systemic chemotherapy in the future[30,31]. Targeted treatment blocks particular pathways useful in cancer initiation and proliferation, resulting in the inhibition of enzymes as well as growth factor receptors required for the evolution of oncogenic cells. Cancer treatment may be substantially better in the future with tailored therapy, and hair loss, the most common adverse effect of systemic chemotherapy, may be decreased.

SMIs: Small molecules are organic chemicals with a low molecular weight that are designed to penetrate the cell membrane, bind particular targets within the cell, and interfere with signaling cascades. The discovery of SMIs was a major breakthrough in cellular biology research. These compounds enable the investigation of numerous biological pathways in order to enhance patient outcomes. Protein kinases linked to cancer initiation and development are key targets in cancer treatment since many SMIs target these kinases. Different proteins and signaling or receptor pathways connected to cancer cells might cause changes in signal transduction cascades. So far, several SMIs with robust and efficient action have been reported, including proteasome inhibitors, VEGF-inhibiting compounds, immune system-regulating drugs, and histone deacetylase (HDAC) inhibitors[32]. Bortezomib, carfilzomib, and ixazomib are examples of proteasome inhibitors. These inhibitors kill pancreatic cancer cells by inducing apoptosis *via* endoplasmic reticulum stress; proapoptotic proteins and their anti-apoptotic target genes are upregulated, whereas numerous anti-apoptotic proteins, as well as signal transducers and transcription activators, are suppressed[33,34]. There was only one randomized study to assess the RR of tumor for bortezomib (PS-341) alone *vs* RR and the survival rate at 6 mo for the combination of bortezomib and gemcitabine in 85 patients with advanced pancreatic cancer. The findings demonstrated that neither bortezomib alone nor in combination with gemcitabine led to an improvement in OS or RR beyond what was anticipated for gemcitabine alone[35]. VEGF-blocking drugs, such as sorafenib and sunitinib, are tyrosine kinase inhibitors used to treat pancreatic cancer. They have two effects: Inhibiting rapidly accelerated fibrosarcoma kinase, which controls cell division and proliferation, as well as the platelet-derived growth factor receptor beta and VEGFR-2 signaling pathways, which block angiogenesis[36] (Figure 2). In a few randomized studies, sorafenib was used to treat advanced pancreatic cancer; however, neither sorafenib alone nor sorafenib in conjunction with gemcitabine showed signs of efficacy that would lead to hope for metastatic pancreatic cancer[37-39]. Sunitinib malate capsules were given

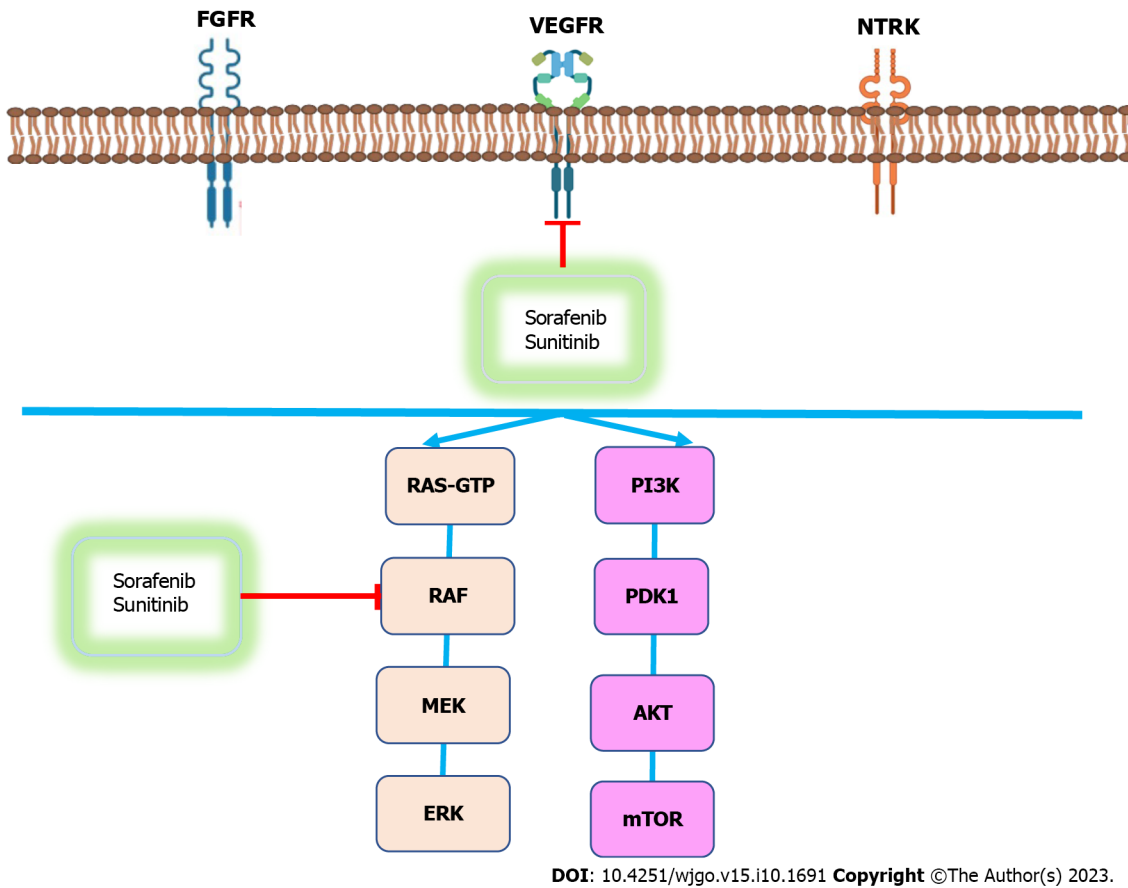


Figure 2 Targeted therapies used in systemic treatment of advanced pancreatic cancers. AKT: Protein kinase B; VEGFR: Vascular epidermal growth factor receptor; ERK: Extracellular signal-related kinase; FGFR: Fibroblast growth factor receptor; GTP: Guanosine triphosphate; MEK: Mitogen-activated protein kinase; mTOR: Mammalian target of rapamycin; NTRK: Neurotrophic tyrosine receptor kinase; PI3K: Phosphoinositide-3-kinase; PKD1: Polycystic kidney disease 1; RAF: Raf proto-oncogene; RAS: RAS proto-oncogene.

Food Drug Administration approval on May 20, 2011, to treat patients with locally progressed or metastatic pancreatic neuroendocrine tumors that are unresectable. One hundred and seventy-one participants were randomly assigned to receive sunitinib (37.5 mg) or a placebo once daily in a phase 3 randomized study. The primary effective outcome was PFS time. OS time, ORR, patient-reported outcomes, and safety were considered secondary goals. For the sunitinib and placebo groups, the median PFS was 10.2 mo and 5.4 mo, respectively. In the sunitinib and placebo groups, the ORRs were 9.3% and 0%, respectively. The OS data lacked maturity[40]. Belinostat, vorinostat, and romidepsin are examples of HDAC inhibitors. They cause cell growth inhibition and apoptosis[41,42]. There has not yet been a randomized control study to assess HDAC inhibitors in advanced pancreatic cancer. SMIs have several advantages over chemotherapeutic drugs and RNA interference agents, including the ability to perform a wide range of *in vivo* assays using different temporal and titration designs, which result in higher penetration in isolation and are useful for testing the combined effects with existing antitumor drugs.

Immunotherapy

The basis for immunotherapy is the distinct antigens that cancer cells release, which T lymphocytes recognize and eliminate. Cancer vaccines enhance the antigen presentation of cancer cells; immune checkpoint inhibitors disrupt the suppressive mechanisms of the immune system that impair effective immunosurveillance of T-cells; and tumor-specific T cells are modified to become more active after being adopted and transplanted. Immunotherapy has been shown in clinical studies to be a possible treatment for numerous solid tumors[43-45]. However, the pancreatic cancer microenvironment, also known as the stroma, contains a variety of noncancer cell components. It has been discovered that stroma, which may account for up to 50% of the overall mass of the tumor in cases with pancreatic cancer, suppresses both naturally occurring and artificially produced antitumor immunity. Immunotherapy for pancreatic cancer is, therefore, extremely challenging. However, there have been several attempts to employ immunotherapy either by itself or in conjunction with other cancer treatment modalities[46].

Immune checkpoint inhibitors: Immune cells include proteins called checkpoints that regulate the immune response. The immune response starts when the checkpoints are activated or deactivated. This process stops immune cells from attacking the body's normal cells, but cancer cells might exploit this defense and evade the immune system. Checkpoint inhibitors interfere with this pathway, causing the immune system to attack tumor cells. These techniques are now being

researched for use in pancreatic cancer. The T-cell immunity inhibitors programmed death-1 (PD-1) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) are the two immunological checkpoints that have attracted the greatest interest. Exocytosis moves CTLA-4 from the naive T cells' intracellular space to their cell surface when they get activated, where it competes with the B7 protein to prevent T cells from becoming activated[47,48]. Numerous immune cells, including T cells, B cells, NK cells, and dendritic cells (DC), express the cell surface receptor PD-1. One of PD-1's ligands, PD-L1, was discovered to be expressed in a variety of cells, including several types of tumor cells. Inhibiting T-cell survival and proliferation, the binding of PD-1 to PD-L1 also allows tumor cells to evade immune surveillance. Upregulation of PD-L1 in pancreatic cancer is associated with tumor growth and a worse prognosis[49].

Anti-CTLA-4 antibodies: Ipilimumab is a anti-CTLA-4 mAb that has been humanized. In a phase 2 study with advanced pancreatic cancer, ipilimumab yielded no response by itself, as measured by the response evaluation criteria in solid tumors (RECIST). In a phase 1 study with previously treated pancreatic cancer patients, ipilimumab was combined with GVAX [granulocyte-macrophage colony-stimulating factor (GM-CSF) gene-transfected tumor cell vaccine]. The efficacy of this combination treatment was demonstrated in this trial as ipilimumab plus GVAX raised median OS (5.7 *vs* 3.6 mo) and 1-year OS rate (27% *vs* 7%)[50] (Table 1). T cell receptor repertoires in peripheral blood from individuals taking ipilimumab with or without GVAX were evaluated using data from the same phase 1 trial. The results demonstrated that participants who had ipilimumab showed more repertoire alterations, particularly when paired with GVAX, which was linked to a much longer life span[51]. Gemcitabine and ipilimumab are a safe and practical treatment option for advanced pancreatic cancer, according to the findings of phase 1 clinical research that examined the long-lasting responses and OS benefit of this combination. Ipilimumab in combination with gemcitabine did not appear to be any more successful than gemcitabine alone in treating advanced pancreatic cancer, despite the fact that one patient in this research had a somewhat persistent response lasting over 20 mo[52] (Figure 3).

A different mAb targeting CTLA-4 is tremelimumab. Tremelimumab plus gemcitabine was well tolerated in a phase 1 investigation with advanced pancreatic cancer, and two participants showed partial responses; nonetheless, this study did not show any RECIST improvement[53]. Tremelimumab did not appear to be beneficial in a separate phase 2 trial in pancreatic cancer patients who had tumor progression after receiving prior conventional first-line 5-FU or gemcitabine-containing treatment[54].

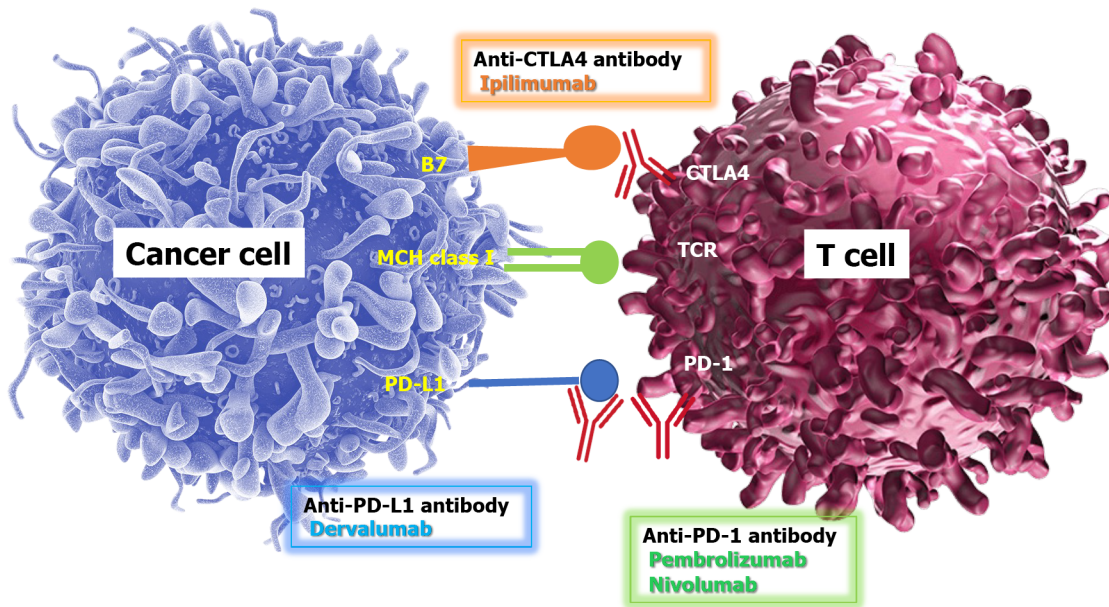
Anti-PD-1 and anti-PD-L1 antibodies: Nivolumab, a monoclonal IG4 anti-PD-1 antibody from human, inhibits the interaction of PD-1 with either PD-L1 or PD-L2. Fifteen pancreatic cancer patients were treated with nivolumab and mogamulizumab, an anti-CC chemokine receptor 4 antibody, in a phase 1 study for patients with advanced or metastatic solid tumors, and only two unconfirmed responses were found[55]. In a multicenter, prospective clinical study, Klein *et al* [56] treated seven advanced cancer patients with pancreatic neuroendocrine neoplasms (NEN) with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 wk for four doses, then nivolumab 3 mg/kg every 2 wk for up to 96 wk, or until severe toxicity or disease progression occurred. They discovered that 43% of pancreatic NEN patients had an objective response. They proposed that combining nivolumab and ipilimumab immunotherapy revealed considerable therapeutic activity in subgroups of patients with advanced, high-grade pancreatic NEN. For 91 advanced pancreatic cancer patients who had not improved after 16 wk platinum-based treatment in 2022, Reiss *et al*[57] conducted a randomized, open-label, phase 1b/2 trial of niraparib with nivolumab or ipilimumab treatment. Using permuted block randomization, the patients were assigned (1:1) to receive four doses of oral niraparib 200 mg daily along with either intravenous nivolumab 240 mg or 480 mg every 2 wk or ipilimumab 3 mg/kg intravenously every 4 wk. They reported that the 6-mo PFS for niraparib plus nivolumab was 20.6% and 59.6% for niraparib plus ipilimumab. They concluded that the main goal was achieved in the niraparib plus ipilimumab maintenance group, while the PFS was reduced in the niraparib plus nivolumab group.

Another monoclonal IG4 antibody from human against PD-1 is pembrolizumab. In a phase 1b study of 11 advanced pancreatic cancer patients, pembrolizumab combined with nab-paclitaxel and gemcitabine produced six cases of stable disease and two cases of partial response. This combination's efficacy was marginally higher than that of gemcitabine combined with nab-paclitaxel in previous studies[58,59]. In comprehensive clinical research involving a variety of cancer types, it was shown that biomarkers related to the clinical success of pembrolizumab included the PD-L1 expression level, T-cell-inflamed gene expression profile, and tumor mutation burden. Patients with pancreatic cancer who received pembrolizumab had an ORR of 0% and an average PFS of 1.7 mo[60]. Another phase 2 clinical trial of pembrolizumab in patients with advanced pancreatic cancer and other solid tumors that are sensitive to the mismatch repair pathway loss-of-function mutations found that the objective radiographic response was 53% and the complete response was 21%[61]. The clinical response was not seen in a phase 1 study that tested the p53-expressing modified vaccinia Ankara virus (p53MVA) alone, but a phase 1 study that combined pembrolizumab with p53MVA showed that three out of 11 patients demonstrated clinical response and the disease was stable for 30, 32, and 49 wk[62,63]. Pembrolizumab was coupled with nab-paclitaxel or gemcitabine in a phase 1/2 clinical study. The OS and PFS were 15.0 and 9.1 mo, respectively, and the disease control rate in the 11 evaluable chemotherapy-naïve pancreatic cancer patients was 100%[59]. In a phase 1, multicenter trial, the monoclonal IG4 antibody from human, BMS-936559, against PD-L1 was investigated for the treatment of several advanced cancers. Patients with renal-cell carcinoma, non-small-cell lung cancer, and melanoma all experienced long-term tumor reduction and stable illness as a result of BMS-936559; however, none of the 14 patients with pancreatic cancer who participated in this trial experienced a response[64]. Furthermore, Mehnert *et al*[65] found that pembrolizumab had anticancer efficacy in a subgroup of pancreatic cancer patients with NETs and was well tolerated. Moreover, to examine the CXCR4 antagonist BL-8040 (motixafortide)'s safety, efficacy, and immunobiological effects when combined with pembrolizumab and chemotherapy, Bockorny *et al*[66] conducted a phase 2a, open-label, two-cohort study in 37 chemotherapy-resistant, metastatic pancreatic cancer patients. They stated that further randomized trials should validate their findings before combining CXCR4 and PD-1 inhibition to treat pancreatic cancer

Table 1 Summary of completed clinical trials investigating immunotherapy in advanced pancreatic cancer patients

Ref.	Drug(s)	No. of patients	ORR (%)	Mean OS (mo)	Mean PFS (mo)	Results
Le <i>et al</i> [50], 2013	Ipilimumab vs ipilimumab plus GVAX	15/15	-	3.6/5.7 1-yr OS (%) 7/27	-	Ipilimumab combined with GVAX was efficacious in advanced pancreatic cancer treatment
Kamath <i>et al</i> [52], 2020	Ipilimumab plus gemcitabine	21	14	6.9	2.78	Gemcitabine plus Ipilimumab is a safe and tolerable regimen for advanced pancreatic cancer with a similar response rate to gemcitabine alone
Aglietta <i>et al</i> [53], 2014	Tremelimumab plus gemcitabine	34	-	7.4	-	Tremelimumab with gemcitabine had a favorable safety and tolerability profile, indicating that it should be studied further in patients with advanced pancreatic cancer
Renouf <i>et al</i> [54], 2022	Gemcitabine, nab-paclitaxel, durvalumab, and tremelimumab vs gemcitabine and nab-paclitaxel	119/61	30.3/23.3	9.8/8.8	5.5/5.4	The results did not demonstrate a benefit from adding durvalumab and tremelimumab to gemcitabine and nab-paclitaxel as a first line therapy in advanced pancreatic cancer patients
Reiss <i>et al</i> [57], 2022	Niraparib and nivolumab vs niraparib and ipilimumab	91 (46/45)	7.1/15.4	13.2/17.3	1.9/8.1	The advantage of niraparib with ipilimumab maintenance treatment extended to patients who did not have known DDR mutations, indicating that the impact is not dependent on DDR deficit
Bockorny <i>et al</i> [67], 2021	Motixafortide, pembrolizumab and FOLFIRINOX	43	13.2	6.6	3.8	In a group with poor prognoses and aggressive diseases, motixafortide and pembrolizumab in conjunction with FOLFIRINOX demonstrated effectiveness. The therapy was well tolerated
O'Reilly <i>et al</i> [69], 2019	Durvalumab vs durvalumab and tremelimumab	64 (32/32)	0/3.1	3.6/3.1	1.5/1.5	The medication was well tolerated, and both durvalumab monotherapy and durvalumab combined with tremelimumab were effective in treating advanced pancreatic cancer patients with a poor prognosis

DDR: DNA damage repair; FOLFIRINOX: Folinic acid, fluorouracil, irinotecan, and oxaliplatin; GVAX: Granulocyte-macrophage colony-stimulating factor gene-transfected tumor cell vaccine; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival.



DOI: 10.4251/wjgo.v15.i10.1691 Copyright ©The Author(s) 2023.

Figure 3 Treatment with immune check point inhibitors for advanced pancreatic cancer. CTLA4: Cytotoxic T-lymphocyte-associated protein 4; MHC: Major histocompatibility complex; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; TCR: T cell receptor.

[67].

Another choice is durvalumab, a monoclonal IgG1 antibody from human that targets PD-L1 and infiltrating T cells in solid tumors. In patients with relapsed or refractory solid tumors, durvalumab was studied in a phase 1b/2 study alongside ibrutinib (a Bruton's tyrosine kinase inhibitor). This study's pancreatic cancer RR was 2% overall, with a median OS of 4.2 mo and median PFS of 1.7 mo. Despite having a good tolerability profile, this regimen had very limited antitumor activity against pancreatic cancer[68]. Another randomized phase 2 study using durvalumab was conducted in individuals with metastatic pancreatic cancer, either alone or in combination with tremelimumab. However, the ORR for individuals receiving tremelimumab plus durvalumab was just 3.1%, and patients treated with durvalumab alone had no response[69]. During a phase 1 study to establish the dose, atezolizumab, an engineered mAb against PD-L1, was found to be well tolerated in a Japanese group[70]. In a phase 1 study for advanced malignancies, atezolizumab was also evaluated in conjunction with navoximod, a small-molecule inhibitor of indoleamine 2,3-dioxygenase 1. There was no evidence to support the addition of navoximod to atezolizumab, but the safety and tolerability of this combination therapy were established, and anticancer efficacy was noted in a variety of tumor types, including pancreatic cancer[71].

Chimeric antigen receptor T-cell therapy

Using modified T-cell receptors or chimeric antigen receptors (CARs), in an effort to target tumor-associated antigens (TAAs), adoptive T-cell immunotherapy, a possible strategy for cancer immunotherapy, alters autologous cells that infiltrate tumors. The optimal target antigen is overexpressed on tumor cells but is seldom or never expressed on normal cells when employed in CAR-T cell therapy. Mesothelin, a cell-surface antigen that is raised in pancreatic cancer but is relatively weakly expressed in the peritoneum, pericardium, and pleura, is the perfect antigen for CAR-T cell treatment [72,73]. A mesothelin-targeted CAR-T-cell therapy has also been demonstrated to be efficient against tumor cells in preclinical conditions, according to several studies. Treatment with modified CAR-T cells targeting mesothelin resulted in strong anticancer action for tumor xenografts and the cell lines of pancreatic cancer[74-76]. In phase 1 research with metastatic pancreatic cancer that had become resistant to chemotherapy, autologous mesothelin-specific CAR-T cells (CARTmeso cells) were found to have potential anticancer benefits and be safe[77]. The cancer stem cell markers CD24 and HER2 are thought to contribute to the emergence of pancreatic cancer[78]. In addition, a phase 1 trial evaluated the safety, viability, and effectiveness of CAR-T cells combined with nab-paclitaxel and cyclophosphamide against HER2 in advanced pancreatic and biliary tract cancers. Five of 11 subjects had stable illness, with a median PFS of 4.8 mo, while one patient had a partial response lasting 4.5 mo. The study established the viability, safety, and the possibility of therapeutic efficacy of HER2-targeting CAR-T treatment[79]. In 60%-80% of pancreatic cancers, prostate stem cell antigen is expressed, but not in healthy tissues. CAR-T cells that target the prostate stem cell antigen have been shown to be beneficial for pancreatic malignancy in two different investigations[80,81]. When used as an antigen in CAR-T therapy, the Tn glycoform of MUC1 demonstrated target-specific cytotoxicity and reduced the development of xenografts made of pancreatic cancer cells[82]. *Ex vivo*-expanded cytokine-induced killer (CIK) cells were used in a phase 2 trial to assess the efficacy and safety of adoptive immunotherapy for advanced pancreatic cancer that is gemcitabine-refractory. The results showed promising improvements in patient quality of life (QoL)[83]. To evaluate the security and efficiency of autologous anti-EGFR CAR T-EGFR cells, Liu *et al*[84] carried out a phase 1 clinical study in patients with advanced pancreatic cancer. Immunohistochemically-detected EGFR expression levels on tumor cells must be over 50%. Six months after being chosen, 16 patients had one to three rounds of CAR T-EGFR cell injection after conditioning with 15 to 35 mg/kg cyclophosphamide and 100 to 200 mg/m² nab-paclitaxel. Grade > 3 adverse effects that might be reversed were fever, tiredness, mucosal or cutaneous toxicities, nausea, vomiting, pulmonary interstitial exudation, and pleural effusion. Eight of the 14 patients who were evaluable had stable disease for 2-4 mo, and four of them saw a partial response. The median OS was 4.9 mo for 14 evaluable patients who were treated with CAR T-EGFR cells for the first cycle, and the median PFS was 3 mo. Lower EGFR expression was seen on tumor cells in patients who experienced stable disease and a reduction in liver metastatic lesions. Additionally, the clinical response was enhanced by central memory T cell enrichment in the injected cells. They claimed that patients with advanced pancreatic cancer can get a safe and effective therapy using CAR T-EGFR cells.

Cancer vaccines

Compared to preventive cancer vaccines, therapeutic cancer vaccines have drawn more attention. Vaccines made from a patient's tumor antigens or cells are known as autologous vaccines, whereas allogeneic vaccines are made from biological material from a different individual. Pancreatic cancer has been the subject of research into many therapeutic cancer vaccines, including whole-cell tumor, DNA, idiotype, DC viral vector, and antigen vaccines[85,86].

Whole-cell vaccines: In a preclinical investigation, increased GM-CSF expression was shown to enhance long-term anticancer efficacy in vaccine-based therapy. As a result, GVAX, the first allogeneic pancreatic cancer whole-cell-based vaccine, was created using two cell lines from pancreatic cancer patients and had been engineered for the expression of GM-CSF followed by radiation to block cell division in the future. In a phase I clinical investigation, GVAX was initially evaluated in people who had their pancreatic cancer surgically removed. The results of this trial showed that GVAX was risk-free, had few side effects, and looked to prolong at least 25 mo for the disease-free time in 4 of the 14 patients who took part in the study[87]. Furthermore, in these three participants, delayed-type hypersensitivity reactions were exacerbated by GVAX. GVAX was investigated in conjunction with cyclophosphamide in patients with advanced pancreatic cancer in a phase 2 study because of the encouraging outcomes. Pancreatic cancer has an elevated level of mesothelin, a tumor differentiation antigen. In this study, mesothelin-specific T-cell responses were seen in the patients who received GVAX treatment and were shown to be improving. GVAX alone or in combination with cyclophosphamide demonstrated no harm. However, as compared to cyclophosphamide alone, the inclusion of GVAX did not appear to

improve median survival[88]. In a phase 2 trial including surgically resected pancreatic cancer patients, GVAX was used as a neo-adjuvant therapy combined with chemoradiation (5-FU-based). Immunotherapy resulted in the discovery that mesothelin-specific CD8⁺ T cells were associated with the disease-free survival rate, and when chemoradiation and GVAX were used together, the OS looked to be better than that in previously reported studies for pancreatic cancer that had been surgically removed. In previously treated pancreatic cancer patients, GVAX was also tried in conjunction with ipilimumab. Ipilimumab with the inclusion of GVAX produced a significant longer median OS and 1-year OS of 5.7 *vs* 3.6 mo and 27% *vs* 7%, respectively[89]. Additionally, in patients with an OS of more than 4.3 mo, the peak number of T-cell repertoire and mesothelin-specific T cells was increased. Further research into how immunotherapy affects pancreatic cancer TME revealed that GVAX treatment upregulated immunosuppressive regulatory mechanisms. This indicates that individuals with pancreatic cancer who have received a vaccination may be better candidates for immune checkpoint and other immunomodulatory therapies, such as PD-1/PD-L1 inhibitors, than vaccine-naïve patients[90]. The efficiency of the *Listeria monocytogenes* expressing mesothelin (CRS-207) and GVAX booster vaccines combined with cyclophosphamide minimum dose was evaluated in advanced pancreatic cancer patients who had previously received treatment. According to this study, CRS-207 and Cy/GVAX heterologous booster had a superior OS than using only Cy/GVAX (6.1 *vs* 3.9 mo) [91]. However, a recent phase 2b, multicenter trial of CRS-207 and GVAX found no survival advantages for the combination of Cy/GVAX and CRS-207 over single-agent chemotherapy in patients with metastatic pancreatic cancer who had previously received treatment[92]. In a phase 1 clinical trial, CRS-207 produced immunological activation, mesothelin-specific T-cell responses, and listeriolysin O, and the participant survival rate was 37% within 15 mo. It was also demonstrated to be safe[93]. Two pancreatic cancer cell lines were altered to generate murine 1,3-galactosyl-transferase to create algenpantucel-L, a second allogenic, irradiated, whole-cell-based tumor vaccine. Adoptive transfer of lymphocytes from mice that received melanoma tumor cell lines as a vaccine in a preclinical animal model expressing β -1,3-galactosyltransferase reduced mouse lung metastases[94]. These findings sparked a phase 2, multicenter study of algenpantucel-L in patients with resected pancreatic cancer receiving gemcitabine- or 5-fluorouracil-based chemoradiotherapy. In contrast to recent trials, which found 45% and 65%, respectively, for the median 1-year PFS and OS, the addition of algenpantucel-L to traditional adjuvant therapy may have improved survival in this trial[95]. In a recent multicenter, phase 3, open-label, randomized trial, algenpantucel-L immunotherapy in combination with standard of care (SOC) chemoradiation and chemotherapy therapy was compared to SOC chemoradiation and chemotherapy therapy alone in 303 Locally advanced or borderline resectable pancreatic cancer patients[96]. They found that the experimental group's median OS was 14.3 mo, whereas the SOC group's median OS was 14.9 mo. The median PFS for the SOC group was 13.4 mo as opposed to 12.4 mo for the experimental group. The researchers found that patients who received SOC chemoradiation and neoadjuvant chemotherapy and had locally advanced unresectable or borderline resectable pancreatic cancer had not a longer OS benefit after algenpantucel-L immunotherapy.

Peptide vaccines: About 90% of pancreatic cancers have KRAS mutations, and the mutant KRAS peptide is presented to CD4⁺ and CD8⁺ T lymphocytes as a foreign antigen. In a recent study, two out of five pancreatic cancer patients who received treatment with a synthetic KRAS mutant peptide showed a brief KRAS-specific T-cell response[97-99]. In a subsequent phase 1/2 pancreatic cancer research trial, 58% (25/43) of patients developed peptide-specific immunity after receiving a KRAS peptide vaccine and GM-CSF adjuvant therapy, which also helped advanced pancreatic patients live longer (146 *vs* 61 d)[100]. Patients with an immunological response to a KRAS peptide vaccination had a 20% 10-year survival rate compared to 0% in a group of pancreatic cancer patients who had not received the vaccine, and this difference persisted more than ten years after the start of long-term follow-up for these patients[101]. In a recent therapeutic study, individuals with resected pancreatic cancer and detected KRAS mutations received GM-CSF treatment plus a KRAS peptide vaccination. Nine patients (or 25%) had an evaluable immune response, of which three had a delayed-type hypersensitivity reaction and one had a specific immune response to their KRAS mutation[102]. Pancreatic cancers have overexpression of mucin 1 (MUC1), a type I transmembrane protein that is highly immunogenic. Various MUC1 vaccine formulations have been tested in phase 1 trials; however, it appears that MUC1-specific T-cell responses are exclusively induced by the vaccination of DC with the MUC1 peptide[103-105]. Gastrin has been linked to both endocrine and autocrine growth pathways and is overexpressed in pancreatic cancer. An antibody response was found in 67% (20/31) of patients in a phase 2 study employing the anti-gastrin immunogen G17DT in advanced pancreatic cancer, and antibody responders lived much longer than non-responders[106]. Patients who had an anti-G17DT response (73.8%) had a significantly higher median survival than non-responders (151 *vs* 82 d) in a different randomized multicenter trial using G17DT[107]. A vaccine that targets telomerase, called GV1001, was made using the human TERT peptide. Patients with nonresectable pancreatic cancer received treatment with GV1001 and GM-CSF in a phase 1/2 study, and the treatment's safety, tolerability, and immunogenicity were assessed. Immune responses that were seen in 24 of 38 individuals and were connected to longer lifespans served as proof of the safety of GV1001[108]. In a phase 3 study, GV1001 was also evaluated in individuals taking gemcitabine or capecitabine for locally advanced or metastatic pancreatic cancer. However, compared to pancreatic cancer patients receiving chemotherapy alone, the incorporation of GV1001 had no positive impact on OS[109]. The identical outcomes were seen in a different clinical experiment as well [110].

DC vaccines: Because the most important antigen-presenting cells are DCs which excite innocent T cells, a DC vaccine is made by loading TAAs *ex vivo* and then reinfusing them into patients. An autologous DC vaccination containing a MUC1 peptide was tested in resected pancreatic and biliary cancers in an innovative phase 1/2 trial. The DC vaccination was well tolerated and had no obvious side effects. Four of the twelve patients were still alive and had no recurrence throughout a follow-up period of more than four years[105]. In patients with resistant pancreatic cancer, a DC vaccination was also examined in conjunction with gemcitabine and/or S-1 treatment. Two of the 49 patients that were included

experienced complete remission, while five others did so partially, and ten had stable disease[111]. Compared to those who received a DC vaccination and chemotherapy alone, patients who also received lymphokine-activated killer cells had a higher rate of survival. This study established the safety and possible efficacy of combining a DC vaccine with chemotherapy in patients with advanced pancreatic cancer who had not responded to standard treatment. In a phase 1 study, poly-ICLC, a Toll-like receptor-3 agonist, was combined with DC-based immunotherapy. The peripheral blood of HLA-A2+ patients was utilized to generate autologous DCs, which were then combined with three definite A2-restricted peptides and was returned to advanced pancreatic cancer patients. On the days of their vaccinations, subjects concurrently got poly(IC:LC) intramuscularly. The median OS for all 12 subjects was 7.7 mo, and of the eight subjects who received imaging on day 56, four had stable disease and four had progression of the disease[112]. An investigation of the clinical outcomes and safety of immunotherapy using DC-CIK in combination with chemotherapy S-1 in pancreatic cancer was the goal of a phase 1/2 trial. In comparison to DC-CIK alone (85 and 128 d), chemotherapy alone (92 and 141 d), or supportive care alone (43 and 52 d), the combination of DC-CIK infusions and S-1 caused importantly longer median PFS and OS (136 and 212 d), proving that it was safe, changed the peripheral blood immune repertoire, and produced a good PFS and OS[113]. In a phase 1 study of patients with pancreatic cancer that was surgically resected, the Wilms' tumor 1 (WT1) peptide was loaded in a DC (WT1-DC) vaccine and evaluated with chemotherapy. There was no discernible toxicity when WT1-DC was combined with S-1 or S-1 with gemcitabine, and seven out of the eight patients had WT1-specific cytotoxic T-lymphocytes[114].

CONCLUSION

Our understanding of the biology of pancreatic cancer has significantly advanced over the past few decades, but tragically, this has not led to a meaningful increase in the therapeutic management of the majority of patients. The aggressiveness of pancreatic cancer and the lateness of its discovery make it very challenging to cure. The majority of patients have advanced stages, which makes therapy difficult. Although advanced pancreatic cancer can be treated with chemotherapy, radiation therapy, and surgery to increase survival and manage symptoms, there is no definite treatment for the disease. The inability of chemotherapy to distinguish between cancer and healthy cells when it targets a range of biological pathways leads to severe side effects. In order to target growth factors, other proteins involved in the development of the illness, and cancer cell surface receptors, therapies based on SMLs and mAbs are necessary. If the condition is discovered quickly and a focused treatment is employed, patients with pancreatic cancer may have a better chance of living. The majority of the targeted treatments investigated for the treatment of pancreatic malignancies have been shown to be unsuccessful, despite the fact that many of them have been developed. There is a need for innovative treatment approaches for pancreatic cancer, such as cancer vaccines, in addition to the conventional targeted medicines and immunotherapies that have been investigated for years. As an alternative, strategies that combine already-existing technology or therapy modalities might also be very helpful, but this would need further investigation and testing.

FOOTNOTES

Author contributions: Leowattana W wrote the paper; Leowattana T and Leowattana P collected the data.

Conflict-of-interest statement: The authors declare no conflicts of interest related to this article.

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