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Review Article

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Immunotherapy and Pancreatic Cancer

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Abstract

Pancreatic cancer is an aggressive and highly lethal form of pancreatic malignancy which is the fourth leading cause of cancer-related deaths in men and women in the USA. According to the American Cancer Society in 2014, it was estimated that about 46,420 people (23,530 men and 22,890 women) were diagnosed of pancreatic cancer. Additionally, in the same year about 39,590 people (20,170 men and 19,420 women) died of pancreatic cancer. It is highly observed men over women and also common with increasing age. The availability of new technology in diagnosis helps in the early detection of the pancreatic cancer. These technologies will serve as the primary requirement for management of disease. The exact cause of pancreatic cancer is not known, several risk factors had been indicated leading to pancreatic cancer. Immunotherapy has been a promising development in the past few years. The recent activities have increased the understanding of the tumor microenvironment, various immunotherapeutic modalities or combination therapy (such as chemotherapy with immunotherapy) had been applied in clinical trial. Additionally, the effects of such modalities in combination with immunotherapy in cancer patients are in still exploratory phase.

Keywords: Pancreatic cancer, K-ras mutations, Cyclin-dependent kinase (CKD) Rb retinoblastoma, Protein phosphorylation, Tumorigenesis, Oncoprotein HDM2, Ductal adenocarcinoma, Pancreatic ductal cancers, Interstitial lung disease (ILD), Adoptive T cell transfer, Ligands, Kinase inhibitors, Monoclonal antibodies, Therapeutic vaccines, Adoptive T cell transfer, Adjuvant immunotherapies, Cytokines, p53 transcription factor pancreatic adenocarcinoma, Immunotherapeutic modalities

Abbreviations: CKD: Cyclin-dependent Kinase; DNA: Deoxyribose Nucleic Acid; FDA: Federal Drug Administration; ILD: Interstitial Lung Disease; MABs: Monoclonal Antibodies

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related deaths in men and women in the USA [1]. Pancreatic cancer is an aggressive and highly lethal form of pancreatic malignancy [2]. Pancreatic tumors usually display ductal, acinar, or endocrine differentiation. The majority (approximately 95%) of pancreatic tumors arises from the exocrine component of the pancreas, and out of these the most common is ductal adenocarcinoma [1].

According to the American Cancer Society in 2014, it was estimated that about 46,420 people (23,530 men and 22,890 women) were diagnosed of pancreatic cancer. Additionally, in the same year about 39,590 people (20,170 men and 19,420 women) died of pancreatic cancer. Pancreatic cancer is more common with increasing age and slightly more common in men than women. Pancreatic cancer accounts for about 3% of all the cancers in the US, and accounts for about 7% of cancer deaths. The average lifetime risk of developing pancreatic cancer is about 1 in 67 (1.5%). In 2011, there were an estimated 43,538 people living with pancreatic cancer in the United States [3].

It includes different types of histopathologic and

genetic characteristics. The availability of new technology in diagnosis helps in the early detection of the pancreatic cancer.

Etiology/Predisposing factors

The exact cause of pancreatic cancer is not known, but there are several risk factors that lead to this disease. Some of these risk factors affect the DNA of the cells of pancreas, which can result in abnormal cell growth and may lead to development of tumors [4].

Factors that increase the risk of pancreatic cancer are as follows:

Cigarette smoking: Smoking doubles the risk of developing pancreatic cancer.

Age: Pancreatic cancer increases with age. More than 80% of the cases develops in between the ages of 60-80.

Race: Pancreatic cancer is more common in the African American population than whites.

Gender: Pancreatic cancer is more common in men than in women.

Chronic pancreatitis: Long-term inflammation of the pancreas (pancreatitis) also increases the risk of developing cancer.

Diabetes: It is a symptom of pancreatic cancer, and long-standing adult-onset diabetes also increases the risk of pancreatic cancer.

Obesity: Obesity may be a risk factor that can develop pancreatic cancer.

Diet: Diet high in meats, cholesterol fried foods and nitrosamines may increase the risk, while diet high in fruits and vegetables reduces the risk of developing pancreatic cancer.

Occupation: Occupation involving exposure to carcinogens such as chlorinated hydrocarbons, formaldehyde, pesticides, organochlorines and other various substances may result in an increased risk of pancreatic cancer and contributes 5% of the overall risk.

Genetics: A number of inherited cancer syndromes increase the risk of pancreatic cancer. These include inherited mutations in the BRCA2, FAMMM, PalB2 or Peutz-Jeghers genes.

Preexisting diseases: All types of chronic pancreatitis (alcoholic, non-alcoholic, hereditary, tropical) have been linked to the subsequent development of pancreatic cancer.

Pathophysiology and molecular basis

More than 85% of pancreatic ductal cancers have an activating point mutation in the K-ras gene at a very early stage of pancreatic-cancer development [5]. The detection of K-ras mutations in the duodenal juice, pancreatic juice, and in the stool of patients with pancreatic cancer has been proposed as an early detection strategy [6,7]. p16, which is a cyclin-dependent kinase (CKD) inhibitor, is altered in up to 85% of pancreatic cancer, resulting in cell cycle progression through Rb retinoblastoma protein phosphorylation [8] in table 1.

Table 1: Commonly altered oncogenes in pancreatic adenocarcinoma [9,10].

Oncogenes	Location of chromosomes
K-ras	12p
HER2/neu	17q
AKT2	19q
MYB	6q

The second most frequently inactivated tumor-suppressor gene is TP53, a well-characterized tumor-suppressor located on chromosome 17p. Its inactivation is a late event in tumorigenesis. The p53 transcription factor is normally maintained at very low level as a result of interaction with the oncoprotein HDM2 (the human homologue of MDM2), which targets p53 for proteosomal degradation. Under conditions of cellular stress, such as genotoxic damage or oncogene activation, the HDM2–p53 interaction is inhibited, and the p53 protein is stabilized. The levels of p53 thus, increases and it regulates a transcription response leading to cell cycle arrest or to apoptosis. After Oncogene-mediated activation, p14ARF protein inhibits MDM2, leading to the stabilization and thus activation of p53.

The MADH4 gene (DPC4 or SMAD4) is inactivated in 55% of pancreatic adenocarcinomas [11]. Like TP53, MADH4 inactivation is a late event in pancreatic tumorigenesis [12-16]. Rozenblum and colleagues noticed that [17], in the comprehensive mutational analysis of pancreatic ductal cancer, all tumors harbor mutations in the K-ras Oncogene. The individual mutational frequencies of

tumor-suppressor genes include: p16, TP53, MADH4, and BRCA2 were 82%, 76%, 53%, and 10%, respectively [18] (Table 2).

Table 2: Commonly altered tumor suppressor genes in pancreatic adenocarcinoma [9,10].

Tumour-suppressor and genome maintenance genes	Location of chromosomes
TP53	17p
CDKN2A*	9p
CDKN2A†	9p
CDKN2B	9p
MADH4	18q
FHIT	3p
RBI	13q
BRCA2	13q
STK11	19q
MAP2K4	17p
ALK5	9q
TGFBR2	3p
TGFBR2§	3p
MLH1	3p

Targeted Therapy

The targeted therapy modalities under clinical investigation for pancreatic cancer are divided into 6 main categories: kinase inhibitors, monoclonal antibodies, therapeutic vaccines, adoptive T cell transfer, adjuvant immunotherapies, and cytokines.

Kinase inhibitors

FDA approved kinase inhibitors

Erlotinib [19]

Indications and use: Erlotinib is a kinase inhibitor and has been received FDA approval for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine.

Contraindications: It is contraindicated in patients with hypersensitivity.

Warnings: It has no black box warning. Common warnings are Interstitial Lung Disease (ILD)-like events, acute renal failure, hepatic failure and hepato-renal syndrome, gastrointestinal perforations.

Adverse Events: The most common adverse reactions (>50%) in pancreatic cancer are fatigue, rash, nausea and anorexia.

Non-FDA approved kinase inhibitors (Table 3)
Monoclonal Antibodies

Monoclonal antibodies (MABs) target specific antigens on tumors. Several MABs are currently being tested in clinical trials:

Non-FDA approved monoclonal antibodies (Table 4)

Bevacizumab: Bevacizumab is a humanized anti-Vascular endothelial growth factor (VEGFO) monoclonal IgG1 antibody approved by the U.S. Food and Drug Administration (FDA) for second-line treatment of advanced glioblastoma multiform as single line treatment and in combination with chemotherapy, it is approved for the treatment of advanced colorectal cancer (CRC), advanced non-small cell lung cancer (NSCLC), metastatic breast cancer (MBC),

Cetuximab: Cetuximab is an epidermal growth factor receptor (EGFR) inhibitor and a recombinant chimeric monoclonal antibody, which has been successfully used in the treatment of the Non-small cell lung cancer, colorectal cancers and squamous cell skin cancer (Non-FDA approved).

Trastuzumab: Trastuzumab is registered for the treatment of human epidermal growth factor receptor (HER)-2+ metastatic breast cancer, for adjuvant treatment of localized HER-2+ breast cancer, and for HER-2+ metastatic adenocarcinoma of the stomach or gastroesophageal junction.

Demcizumab: It is a humanized monoclonal antibody which blocks Delta-like ligand 4 (DLL4), a ligand of Notch receptors. Notch signaling has been implicated as a key signaling pathway in cancer stem cells. By treating patients with a combination of Demcizumab and a cytotoxic chemotherapy.

Vantictumab: Vantictumabis a human IgG2 monoclonal antibody designed for the treatment of cancer by inhibiting 'wntsignalling pathways' by targeting the frizzled receptors on cancer cells.

Table 3: Non-FDA approved kinase inhibitors [20-31].

Kinase inhibitors	Clinical trial identifier no.	Phase	Study design	Target
Ruxolitinib	NCT02117479	Phase III	Randomized, Double blind	JAK
X-82	NCT01784861	Phase I/ II	Non-Randomized, Safety/Efficacy Study, open label	VEGFR
Dinaciclib	NCT01783171	Phase I	Randomized, Safety/Efficacy Study, open label	Cyclin dependent kinase
Sphingosine kinase-2 inhibitor ABC294640	NCT01488513	Phase I	Safety Study, open label	SK2
Sorafenib	NCT00541021	Phase III	Randomized, Double blind	RAF kinase
Trametinib	NCT02079740	Phase I, Phase II	Safety/Efficacy Study, open label	MEK MAPK/ERK kinase
Vandetanib	NCT01601808	Phase II	Randomized, Safety/ Efficacy Study, Double blind	VEGFR2
Dasatinib	NCT01652976	Phase II	Safety/Efficacy Study, open label	Tyrosine kinase
Regorafenib	NCT02080260	Phase II	Efficacy Study, open label	VEGFR 2 and 3, and Ret, Kit, PDGFR and Raf kinases
Cabozantinib	NCT01663272	Phase I	Safety Study, open label	RTKs
Alisertib	NCT01924260	Phase I	Safety Study, open label	Aurora K kinase
Momelotinib	NCT02244489	Phase I	Non-Randomized, Safety Study, open label	JAK1/2

Table 4: Non-FDA approved monoclonal antibodies [32-42].

mAbs	Clinical trial identifier no.	Phase	Study design	Target
Bevacizumab	NCT00088894	Phase III	Randomized, Safety/Efficacy Study, double blind	VEGF
Cetuximab	NCT00871169	Phase II	Efficacy Study, open label	EGFR
OMP-59R5	NCT01647828	Phase I/II	Randomized, Safety/Efficacy Study, double blind	Cancer stem cell
IMMU-132	NCT01631552	Phase I, Phase II	Safety/Efficacy Study, open label	Trop-2
MM-151	NCT01520389	Phase I	Non-Randomized, Safety Study, open label	EGFR
IMMU-107	NCT01956812	Phase III	Randomized, Efficacy Study, Double blind	MUC1 antigen
Trastuzumab	NCT00923299	Phase I/II,	Non-Randomized, open label	HER2
NPC-1C/NEO-102	NCT01040000	Phase I, Phase II	Safety/Efficacy Study, open label	CPAAs
MLN0264	NCT02202785	Phase II	Efficacy Study, open label	GCC
Demcizumab	NCT01189929	Phase I	Non-Randomized, Safety/Efficacy Study, open label	DLL4
Vantictumab	NCT02005315	Phase I	Non-Randomized, Safety/Efficacy Study, open label	CSC

Vaccine based immunotherapy

Several trials of vaccines, given alone or with other therapies, are currently enrolling patients with pancreatic cancer.

Non-FDA approved Vaccines (Table 5)

Adoptive cell therapy

Another major opportunity of immunotherapy for pancreatic cancer is adoptive T cell transfer. Several trials of adoptive T cell transfer techniques are currently on the way for patients with pancreatic cancer, including:

Non-FDA approved adoptive T cell therapy (Table 6)

Adjuvant immunotherapies

Adjuvants are used alone or in combination with other immunotherapy. Some adjuvant immunotherapy use ligands. These ligands may be stimulating (agonists) or blocking (antagonists).

Non-FDA approved adjuvant therapy (Table 7)

Cytokines

Cytokines are messenger molecules that help control the growth and activity of immune system cells.

Non-FDA approved cytokines (Table 8)

Checkpoint inhibitors

Non-FDA approved checkpoint inhibitors (Table 9)

Conclusion

There is a strong rise in immunotherapy options for resilient cancers like pancreatic adenocarcinoma. Our success in treating pancreatic cancer is increasing and advancing with the knowledge of the function of the immune system. Immunotherapy has been a promising development in the past few years. The recent activities have increased our understanding of the tumor microenvironment, various immunotherapeutic modalities or combination therapy (like chemotherapy with immunotherapy). Additionally, the effects of such modalities in combination with immunotherapy in cancer patients are still exploratory phase. The complete perspective of immunotherapy treatment has not been realized and utilized. Proper preclinical and clinical designs are the important pillars in understanding the future of immunotherapy in treating cancer patients.

Table 5: Non-FDA approved vaccines [43-49].

Drug	Clinical trial identifier no.	Phase	Study design	Target
Algenpantucel-L	NCT01836432	Phase III	Randomized, Safety/Efficacy Study, open label	Block tumor growth
GVAX	NCT02004262	Phase II	Randomized, Safety/Efficacy Study, open label	Block tumor growth
NY-ESO-1 reactive TCR	NCT01697527	Phase II	Safety/Efficacy Study, open label	NY-ESO-1
DCVax	NCT01882946	Phase I, Phase II	Safety/Efficacy Study, open label	Reduce tumor growth
DEC-205-NY-ESO-1 fusion protein vaccine	NCT01522820	Phase I	Non-Randomized, Safety Study, open label	NY-ESO-1 (cancer testis antigen)
Survivin peptide vaccine	NCT00108875	Phase I, Phase II	Non-Randomized, Safety/Efficacy Study, open label	T cell
Autologous gp96 vaccination	NCT02133079	Phase I, Phase II	Safety/Efficacy Study, open label	T cell
PANC 10.05 pcDNA-1/GM-Neo and PANC 6.03 pcDNA-1 neo vaccine	NCT01088789	Phase II	Randomized, open label	GM-CSF

Table 6: Non-FDA approved adoptive T cell therapy [50-55].

Drug	Clinical trial identifier no.	Phase	Study design	Target
CAR T cells	NCT01583686	Phase I/II,	Non-Randomized, Safety/ Efficacy Study, open label	Mesothelin
TIL	NCT01174121	Phase II	Non-Randomized, Safety/ Efficacy Study, open label	Cancer cells
Anti-NY ESO-1 mTCR PBL	NCT01967823	Phase II	Non-Randomized, Safety/ Efficacy Study, open label	NY-ESO-1
Anti-MAGE-A3-DP4 TCR	NCT02111850	Phase I/II	Non-Randomized, Safety/ Efficacy Study, open label	MAGE-A3-DP4
CAR T cells	NCT01218867	Phase I, Phase II	Non-Randomized, Safety/ Efficacy Study, open label	VEGFR2
NY-ESO-1 reactive TCR	NCT01697527	Phase II	Safety/Efficacy Study, open label	NY-ESO-1

Table 7: Non-FDA approved adjuvant therapy [56].

Drug	Clinical trial identifier no.	Phase	Study Design	Target
Entolimod	NCT01527136	Phase I	Safety Study, open label	Block tumor growth

Table 8: Non-FDA approved cytokines [57].

Drug	Clinical trial identifier no.	Phase	Study design	Target
AM0010	NCT02009449	Phase I	Non-Randomized, Safety Study, open label	Block tumor growth

Table 9: Non-FDA approved checkpoint inhibitors [58-61].

Drug	Clinical trial identifier no.	Phase	Study design	Target
Ipilimumab	NCT01473940	Phase I	Safety study, open label	Block tumor growth
MEDI4736	NCT01693562	Phase I, Phase II	Non-Randomized, Safety/Efficacy Study, open label	PD-L1
Nivolumab or Nivolumab + Ipilimumab	NCT01928394	Phase I, Phase II	Randomized, Efficacy Study, open label	Block tumor growth
Pembrolizumab	NCT02305186	Phase I, Phase II	Randomized, Safety/Efficacy Study, open label	PD-1

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