

Pancreatic Ductal Adenocarcinoma and its Treatment Strategies

Aiman Yaseen¹, Muhammad Akram^{1,*}

¹Department of Life Sciences, School of Science, University of Management and Technology, Lahore, 54770, Pakistan

*Corresponding Author: muhammad_akram@umt.edu.pk

Abstract

Pancreatic ductal adenocarcinoma (PDAC) is one of the lethal malignancies due to the complex biology, genetic factors, over - expression of multiple biomarkers leading to multiple signaling pathways, immersed nature of tumor, lessen survival incidence from surgical resection and delayed diagnosis. The conventional treatment methods with less efficacy include chemotherapy and combinational therapy of gemcitabine with other chemotherapeutic drugs. These are some factors which demands advanced therapeutic regimens which includes oral drug which can stop progression at early stages. To address this concern, different drugs have been identified through virtual screening and experimented *in-vivo* and *in-vitro* that showed effective treatment outcomes. Capecitabine combination with different drugs has shown promising results in case of combinational therapies usage against PDAC. Advanced treatment strategies includes immunotherapy, use of monoclonal antibodies, immune checkpoint inhibitors, cancer vaccines, personalized medicine and nanotechnology based drug delivery system (DDS) which opens doors for rapid and promising results to alleviate progression of pancreatic ductal adenocarcinoma. Drug delivery through nanotechnology based drug delivery system (DDS) has been showing effective anti-tumor results to stop the progression of cancer at advanced stage of PDAC. Overall, this review suggested that advanced technologies could serve as a robust way to treat this solid malignancy as well as development of drugs (oral / effective chemotherapeutic drug) can stop this disease at early as well as at advanced stages.

Key words: PDAC, gemcitabine, capecitabine, immunotherapy, nanotechnology- based drug delivery system (DDS)

1. Introduction

Pancreatic cancer is one of the leading cause of deaths around the globe. Pancreatic ductal adenocarcinoma (PDAC) is one of the common type of pancreatic cancer. Reports on statistical analysis of Globocan 2020 [1] on pancreatic cancer showed that it stands at 7th position due to its high mortality rate. As a result, it is estimated that it will surpass lung cancer in the next 20 to 30 years. Around 4 million deaths have been reported to occur in 2020 [2]. It is expected that it would be ranked at 2nd position by the end of 2040 due to its fatality [3]. For past 20 years, gemcitabine has been used for treatment of pancreatic ductal adenocarcinoma [4]. Due to its short-term anti-cancer effects, other drugs combinations has also been in use which includes FOLFIRINOX, CISPTALIN and CAPECITABINE [5]. These drugs enhanced the magnitude of treatment outcome but unable to attain complete removal of cancer. Moreover, the survival rate is also low after obtaining surgical resurrection of tumor, only 9% survival rate is reported in surgical removal of tumor. Mostly, it is diagnosed at 4th stage of cancer, till that time it has spread in the body; that is why it has become malignant due to its metastasis [2]. The common genetic mutation include oncogene KRAS and suppression of



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tumor suppressing genes such as *CDKN2A*, *SMAD4* and *TP53* [6]. There are some other problems which has been reported during examination in clinical trials. It includes delayed diagnosis, resistance to chemotherapy [7] and difficulty in obtaining the tissue sample of pancreas due to the immersed nature of tumor [8]. Due to the occurrence of disease, prominent changes are observed during histology and in studying molecular mechanism of pancreatic duct cell lining. As a result, healthy cell lines changes into pancreatic intraepithelial neoplasia which leads to invasive carcinoma and pancreatic ductal adenocarcinoma [9]. For resection of tumor, surgery is done as a primary treatment followed by chemotherapy with adjuvant therapy. Approximately 10% to 20% cases are liable for surgical resection [10]. There is an urgent need to develop novel and robust technologies which will find applications in removal of different types of tumors at multiple stages of pancreatic ductal adenocarcinoma.

Revolutionary development in the field of drug discovery is dated back to 1928 when Alexander Fleming discovered Penicillin. This discovery revolutionized the pharmaceutical industry, medical field and global healthcare sectors. Consequently, this drug development influenced the field of biochemical research and drug discovery which have profound impact on all mankind, saving their lives and leading to the development of antibiotics [11]. In the field of drug development and discovery, biochemistry, novel technologies are necessary for elucidating the underlying molecular mechanisms of disease progression. This plays a crucial role in identifying the potential targets or biomarkers to design effective therapeutic regimens [12]. Drug design paves the way for the science of pharmaceutical chemistry that finds its applications in biochemistry, toxicology, pharmacy and oncology [13].

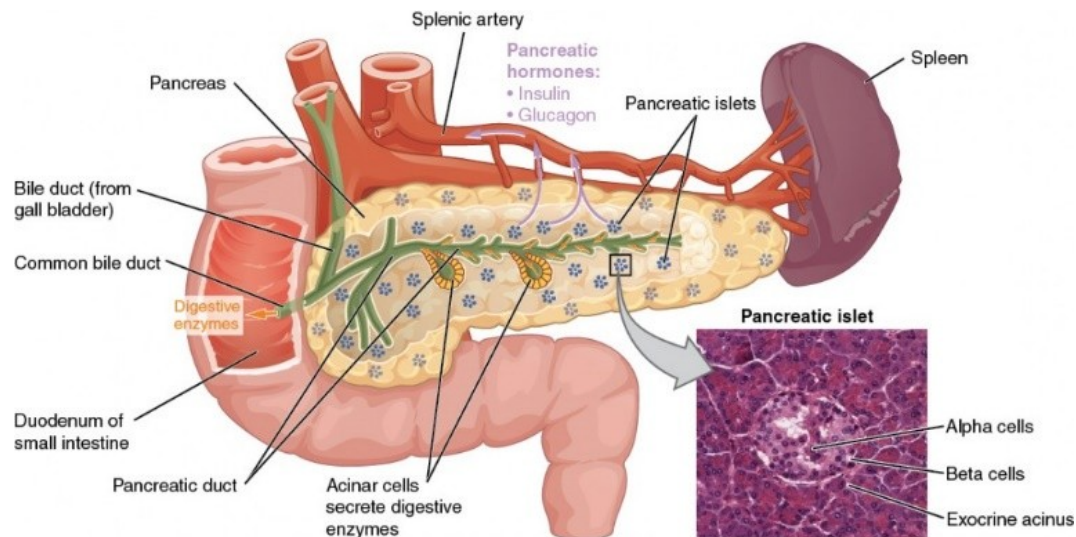
Identification and validation of target is one of the important biochemical techniques which ensure that drug with alter the function of target by showing efficacy and becoming a promising treatment [14]. Due to poor prognosis and aggressive nature of pancreatic ductal adenocarcinoma, there is a pressing need for advanced, novel and effective treatment strategies, which include drug discovery and development for early recovery from PDAC, nanotechnology, based drug delivery system and personalized medicines. There are different biomarkers and multiple genes which are over-expressed during pancreatic cancer, serve as an identification target to design drug by utilizing novel technologies for improving the efficacy of treatment [15].

Computer aided drug design (CADD) has revolutionized the world by utilizing the techniques such as X-ray crystallography (X - ray) and nuclear magnetic resonance (NMR) to find the structure of targets which helps in providing the detailed information about the structure of the target protein and hence enables to design drugs which specifically binds to the target [13]. Immunotherapy also unleashes a new way to serve as better treatment option as compared to conventional methodologies. Additionally, the concept of personalized medicines and used of nanotechnology based drug delivery system has revolutionized the way to overcome the complex biology of PDAC.

Drug discovery and development through different technologies and strategies has addressed multiple diseases such as Alzheimer's disease, Parkinson's disease, many viral diseases and multiple types of cancers such as prostate cancer, ovarian cancer, breast cancer, lung cancer, pancreatic cancer and many more. This review aims to discuss the biology and treatment strategies for pancreatic ductal adenocarcinoma.

2. Physiology of Pancreas

This is an organ present behind the stomach surrounded by other organs. It has a major role in digestion, comprises of enzymes like amylase, trypsin and lipase. It is made up of two glands endocrine and exocrine glands.



3. Literature Review

After conducting thorough literature review, pancreatic cancer is regarded as one of the fatal malignancy of gastro- intestinal (GI) tract. When 90% of the cancer has metastasized, then it is diagnosed. That is why it shows resistance to complete removal and as a results cause deaths in ~ 90% of cases. Though surgical removal and chemotherapy are available but 5% survival rate is reported and chemotherapeutic drugs shows less results due to its immersed nature [8].

3.1. Proteins over-expresses during PDAC

There are multiple novel tumor specific proteins, genes or antigens which are crucial for the point of view of therapeutic applications in PDAC. Here in this review, a few proteins are being discussed, their function, importance in the progression of PDAC.

3.1.1. Leukemia Inhibitory Factor (LIF)

Leukemia Inhibitory factor (LIF) has been recently identified as a therapeutic, circulating biomarker, over-expresses during PDAC [16]. It is significantly important because it is sensitive and superior biomarker than cancer-antigen (CA 19-9) and cancer embryonic antigen (CEA) of pancreatic cancer. Studies showed that its expression significantly increases during PDAC. LIF works by binding onto the receptor leukemia inhibitory factor receptor (LIFR) present on pancreas, form glycoprotein (gp-130) complex and start phosphorylation of signaling molecules and transcription of transcription factor in the downstream [17]. As a result, multiple pathways starts which starts progression of PDAC [18].

3.1.2. Nima -related protein kinase -7 (NEK-7)

Another protein has been reported which showed to overexpress in PDAC. NEK7 binds to NLRP inflammasome and starts cell cycle and spindle formation, more tumor cells will be formed and cancer progresses [19].

3.1.3. Phosphoprotein Phosphatases family (PPPs)

PPP1CA is a member of PPPs which is involved in de-phosphorylation of p53- a tumor suppressor gene and it is concerned with glycogen metabolism, cell cycle progression and gene transcription during PDAC [20].

3.1.4. Kallikrein -related protein -8 (KLK8)

KLK8 is also an important protein which over-expresses during PDAC. Over-expression of this protein cleaves epidermal growth factor (EGF), then binds to epidermal growth factor receptor (EGFR) and start multiple signaling pathways associated with the progression of PDAC.

3.2. Treatment Availability of PDAC

There are different clinical trials of different drugs are in phase 1 and phase 2. Cabiralizumab plus nivolumab in combination of gemcitabine are in phase 1a and phase 1b for treatment of pancreatic cancer [21]. If cancer is in stage 2, stage 3 and stage 4 gemcitabine hydrochloride is in use. Olaparib, Mitomycin as oral drugs are also reported which are in used against this cancer. Durable results have been reported but no acceptable profile has been reported [5].

3.2.1. Non- oncology Drugs for PDAC

There are some non-oncology drugs which are prior used for treatment of other diseases. In a recent study, the mechanism of these non-oncology drugs are modulated to resonate them with already available data on preclinical and clinical trials for pancreatic cancer as they showed promising results [22]. Figure 2 is showing the complex tumor microenvironment of pancreatic cancer cells which include pancreatic cancer stem cells (Pa- CSCs), cancer associated fibroblasts (CAFs), pancreatic stem cells (PSC), myeloid derived suppressor cells (MDSC), tumor associated macrophages (TAM), tumor associated neutrophils (TAN). There is a complex cross talk among the cells and cell component of PDAC.

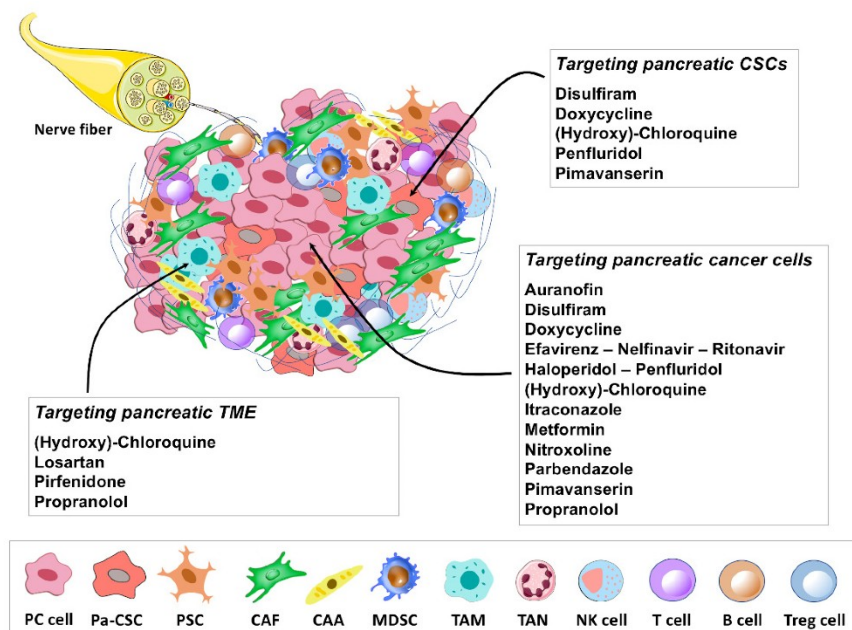


Figure 2. Microenvironment of Pancreas

3.2.2. Drugs obtained through Virtual Screening

There is a comprehensive number of drugs obtained through virtual screening available. A study reported in 2020 [17] that EC359 has shown to inhibit the signaling pathway initiated by LIF. Molecular docking of EC359 has shown to inhibit the LIF/LIFR signaling, as it showed anti-proliferative effects, apoptosis of cancer and reduced the invasiveness of cancer. *In-silico* drug identification of NEK7 has come in light in which Dacomitinib and Neratinib – food and drug administration (FDA) approved drugs showed promising results. In another study, Phenylcarbamoylpiperidine 1,2,4-triazole amide derivatives were docked with the target

NEK7 protein [23]. Recent study on *in-silico* analysis of NEK7 and PPP1CA showed that a phytochemical Boeravinone has been identified which can slow the progression of PDAC. But its efficacy for *in-vivo* and *in-vitro* studies need to be conducted [24]. An *in-silico* study published in 2019 reported that ZINC02927490 can act as a promising inhibitor of KLK8 [25]. Resultantly, it can stop progression of cancer such as ovarian cancer [25], [26], pancreatic ductal adenocarcinoma [27] and other neurological disorders which includes Alzheimer's disease [25], [28]

3.2.3. Chemotherapy

There are different combination of chemotherapeutic drugs for different types and stages of PDAC. Currently approved therapies include chemotherapy [29] which uses **gemcitabine** as a chemotherapeutic drug. This is used alone as well as in combination with capecitabine and nab-paclitaxel for the treatment of different stages of tumor in pancreas [30]. Capecitabine is also administered as an adjuvant therapy if tumor is resectable and sometimes used in combination with radiotherapy if the tumor is unresectable [30]. Another drug nab-paclitaxel is used in combination with gemcitabine if patient doesn't tolerate FOLFIRINOX. This is used for the patients having metastatic PDAC. It works by disrupting microtubule functioning during spindle formation in mitosis [31]. For the first-line treatment of metastatic PDAC, FOLFIRINOX, is a combination therapy consisting of 5-fluorouracil, folinic acid, oxaliplatin, and irinotecan [30] [32].

3.2.4. Surgical Treatment

Conventional chemotherapy provided less survival benefit, then only curative realistic option left for PDAC patients is complete resection and adjuvant therapies. Tumor localization and extension determines the choice of surgery. Pancreaticoduodenectomy (head/body of the pancreas and nearby organs are removed) [33], distal pancreatectomy (tail, body and spleen) [34], total pancreatectomy (whole pancreas and nearby organs) [35] or palliative surgery (stent or bypass) [36], are some options which are available for those patients who are willing for surgical resection. These types of surgical resection may alleviate symptoms of obstruction present in biliary parts of gastro-intestinal tract. One of the crucial factor for the success of surgery is R0 resection, which mean to clear margins. This is important in case of pancreaticoduodenectomy and distal pancreatectomy [37]. Some prognostic factors assess the patient's outcomes, eligibility of the surgical treatment and to monitor disease progression. These include extent of venous involvement, size of tumor, and loss of blood during surgery, resection type (R0, R1/R2 resection), expertise of surgeon and rate of tumor recurrence which influence the surgical resection [38].

4. Combinational Therapies

Different combination therapies employed after the approval of gemcitabine as a chemotherapeutic drug. These combination therapies utilized different cytotoxic and biological agents. However, these therapies were also showing less benefit. Combination of PEFG (cisplatin, epirubicin, 5-fluorouracil [FU], gemcitabine) regimen and S1 gemcitabine [39] showed anti-tumor effects but caused toxicity [40]. Other food and drug administration (FDA) approved drug includes gemcitabine or erlotinib provides modest survival improvement against EGFR but showed hypersensitive reactions such as rashes. Capecitabine combination with oxaliplatin, erlotinib, gemcitabine, docetaxel and chemoradiation showed promising response with anti-tumor effects against localized pancreatic cancer [41]. In nutshell, these combination therapies showed mixed results depending upon the situation.

5. Immunotherapy

An advanced type of cancer treatment is immunotherapy. Tumor microenvironment (TME) consists of different types of cell populations, which include dendritic cells, (CAFs) cancer associated fibroblasts, epithelial cells, T-regulatory cells, tumor associated macrophages (TAM), and B-lymphocytes. They show intrinsic resistance to conventional treatment that is use of chemotherapeutic drugs. Several types of immunotherapies reported such as use of monoclonal antibodies, immune checkpoint inhibitors, adoptive cell transfer and vaccination.

CTLA-4 an immune checkpoint it inhibit to stop cancer progression. It over-expresses and stops T-cell to function in killing of cancerous cells. Anti-CTLA-4 antibody ipilimumab [42] is introduced in mouse models with PDAC showed good response [43], but it is non-responsive in case of solid PDAC in humans. However, this drug is available; more research needed to study its mechanisms so that it will activate the T- cells to kill the cancerous cell. This is one of the application of monoclonal antibodies. Another study suggested that use of anti-IL-6 and anti-CTLA-4 promotes anti-tumor activity of pancreatic cancer cells, thus activated T-cells [44].

The basic purpose of giving immunotherapy is to stimulate immune system to activated T cell. Different drugs which are immune checkpoints inhibitors are in use for different other tumors but no promising results are still available for PDAC. This resistance is happening due to the dense TME of pancreatic cancer cells. Another inhibitor of immune checkpoint is reported which is programmed death PD-1 which binds to its receptor programmed death ligand 1 (PD-L1) [45]. This is expressed on the surface of pancreatic cancer cell and forms heterodimer with CD80 as well as activates T-cell [46] [47]. But this is also unresponsive towards advanced stage of tumor and results in poor prognosis of cancer [45] [48].

Another approach in immunotherapy is being introduced named adoptive cell transfer which aims to add immune cells such as natural killer cells which will improve patient's immune system and combat like natural immunity. This approach has been conducted in PDAC mouse models and increased necrosis of tumors cells has been showed with effective results. This is the only study conducted with this technology for combating PDAC tumor, more research is needed in future for treating PDAC in humans [49].

Cancer treatment vaccines are also available to be given to patients to prevent ant remnants of post-surgery. These vaccines uses whole – tumor cell lysate and iPSC which target tumor associated antigen that initiate immune response with improving survival in PDAC murine models. These cancer treatment vaccines are useful in preventing tumor relapse and reverse immunosuppression of TME [50].

6. Nanotechnology based drug delivery system (DDS)

A novel nanotechnology based drug delivery system (DDS) has been introduced to enhance the therapeutic outcomes of PDAC patients. This DDS aims to deliver a nano-particle based drug which binds to its receptor present in the micro-environment of cancer cells. A recent study has been conducted which designed combination of different drugs analog of somatostatin and packed them in paclitaxel loaded liposomes which delivered that drug to the respective ligand i.e., somatostatin receptor. These DDS showed anti-tumor effects, slower the angiogenesis, and equally effective in suppressing the growth of tumor [51].

7. Personalized Medicines

Molecular guided based medicines which aims to address the particular genetic change comes under personalized medicines. A study conducted to check the mutations common in PDAC patients showed feasible results when given with personalized medicines. The mutations include were *KRAS*, *TP53*, *CDKN2A*, *SMAD4*, *NOTCH1*. Personalized medicine such as mTOR inhibitors (pembrolizumab, palbociclib, nintedanib, cetuximab, crizotinib, tamoxifen, and the combination of lapatinib and trastuzumab) to different patients separately. The one patient given nintedanib showed stable disease for 6 months [52]. Another study reported that supports that nintedanib has robust anti-tumor effects especially when given in combination with gemcitabine – in an *in-vivo* setting [53].

As mentioned so far, PDAC is one of the lethal malignancy with a survival rate less than 10%. For over 20 years, a conventional chemotherapeutic drug is being used i.e., gemcitabine having less efficacy and survival benefit. Research has been carried out to design effective treatment regimens. There are some check point kinase (ChK1) inhibitors, *KRAS* (Kirsten rat sarcoma viral oncogene homolog) antibody/MEK (mitogen-activated protein kinase- kinase) inhibitors, autophagy inhibitors and combination of gemcitabine with natural products are reported. Significant tumor reduction has been seen due to the combinatorial usage of ChK1 inhibitors and gemcitabine. It can reduce tumor initiating capacity of pancreatic cancer cells [54]. Another study conducted in 2018 confirms that an *in-silico* identified drug along with wet lab experimentation has showed that Cryptotanshinone resulted in enhanced cell death of humans cancer cell lines in pancreas [55]. Some novel formulations of liposomes needs to be validated for further research in the field of nanotechnology based drug delivery system (DDS) [51].

There are some limited regarding the treatment strategies of PDAC. Prior, only gemcitabine was used. Some other combinations were also used but there are some limitations in using these drugs as combinational therapies. Some non-oncology drugs, *in-silico* identified drugs are also available but they lack *in-vivo* and *in-vitro* experimentations for proper validation to be used as a treatment against PDAC. Personalized medicines have some limitations too. They will target specific mutation or specific biomarkers. It means huge amount of funds are required for designing medicines for other mutations or genes which are leading towards PDAC. Advanced treatment such as nanotechnology based drug delivery system (DDS) has outperformed conventional treatment in clinical trials. But it also require further research to develop formulations that target every specific mutation. This requires a lot of research to explore the unidentified and unexplored areas.

8. Conclusion

Progress in the treatment of PDAC is ongoing and survival rate has been increased from 5% to 9% from the last few years. Since 1996, the treatment against PDAC has started and emerging day by day that will improve the outcome of the disease to overcome it. But gemcitabine and combination of different drugs has not shown survival benefit. Combination use of monoclonal antibodies and immune checkpoint inhibitors have shown proven results yet. Still, there is an urgent need to develop strategies that would discover specific and sensitive biomarkers for rapid identification. There is a need to conduct more pre-clinical and clinical studies to explore the efficacy of different treatments. Advanced treatments such as immunotherapy, personalized medicines and nanotechnology based drug delivery system has revolutionized the field of drug development and discovery that will target the specific genes and receptors, ultimately stop the signaling pathways and hence alleviate disease progression. There is a need to collaborate with different oncologist, pharmacists,

radiologist and surgeons to design the accurate patients' classification for proper treatment at proper time. Research is needed to further explore the best treatment in the recent years to combat this lethality.

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