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Pancreatic Ductal Adenocarcinoma: Current and Emerging Treatments

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ABSTRACT

Pancreatic Ductal Adenocarcinoma (PDAC) is a deadly disease with increasing incidence and mortality rates. The most effective treatment for Pancreatic Ductal Adenocarcinoma is surgery, but because of the late-stage diagnosis which is typical among PDAC patients, as well as poor imaging technology, surgery is not a viable option for 80-85% of patients. Therefore, the most common treatments for PDAC currently are Chemotherapy, Immunotherapy, and Radiotherapy. Chemotherapy for PDAC is performed with a combination of drugs. The current standards of chemotherapy drug combinations are being challenged and new chemotherapy combinations are under clinical trial. Immunotherapy for PDAC consists of immunomodulators, oncolytic viruses, adoptive cell therapies, and cancer vaccines. Recently, a shift of focus within PDAC immunotherapy research has yielded an emphasis on protein inhibition. A new protein inhibition strategy is under clinical trial. Radiotherapy is rarely used to treat PDAC in recent years, but there is an emerging hypothesis implying that radiotherapy may be used on tumors to kill tissue that may not be removed via surgery. The future of PDAC treatment is unpredictable - because of the high mortality rate and low survival rate relative to other cancers, researchers are forced to think creatively and pursue treatments different than those of other cancers. The likelihood of improvement in PDAC treatment is great because of the current poor standard and the vast amount of emerging research.

Overview

Pancreatic cancer is the fourth leading cause of cancer death in the United States and the incidence of pancreatic cancer in the United States has increased by about 1% each year since 2001 while the mortality rate has increased .3% each year since 2001 (Nikšić et al., 2023). There are three histologic subtypes of pancreatic cancer: adenocarcinomas, neuroendocrine neoplasms, and unclassified. Pancreatic ductal adenocarcinoma (PDAC) is the most common histologic type of pancreatic cancer and is responsible for 300,000 deaths per year. PDAC is expected to be the leading cause of cancer death in the United States by 2030 (Schawkat et al., 2020).

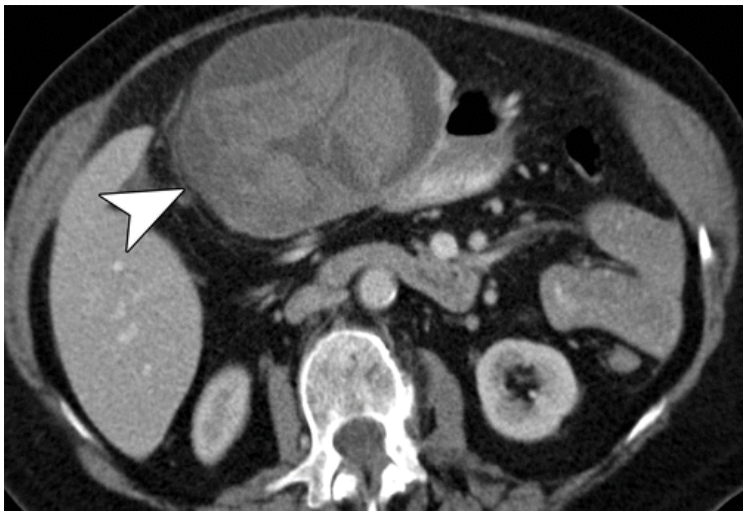

Figure 1. A CT scan of a 61-year-old trauma patient is shown. The patient had a small pancreatic hematoma (blood clot), signified by the arrow, as well as a small mass (not shown). These irregularities are signs of PDAC, but because no PDAC-related symptoms were exhibited by the patient, the PDAC was left undiagnosed and untreated.

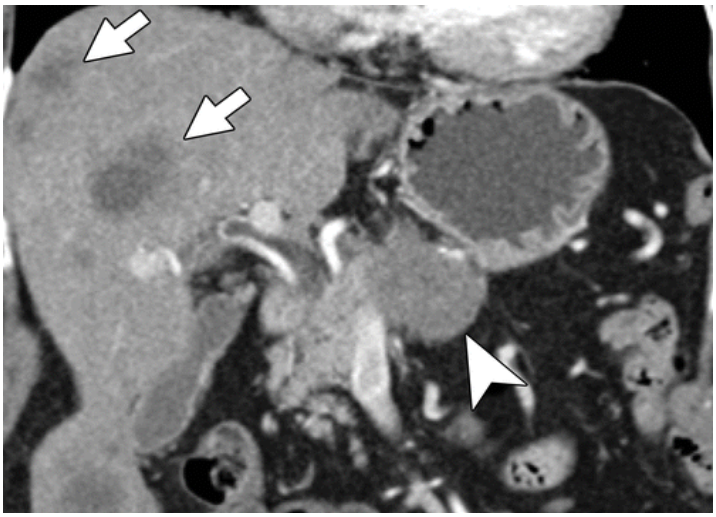

Figure 2. A CT scan of the same patient referred to in Figure 1 is obtained 12 months later. In this figure, PDAC symptoms had only begun to occur. By the time this CT scan was taken, metastasis (as shown by arrows) had already occurred, leaving the patient with unfavorable odds of survival. Should the CT scan shown in Figure 1 have been observed and interpreted correctly, PDAC would have been diagnosed earlier, giving the patient a better chance at survival

The symptoms of PDAC are typically unspecific and the microscopic tumors that develop into PDAC are typically not detected through observing medical imaging, as seen in Figure 1, unless done retrospectively. As seen in Figure 2, PDAC is often diagnosed after the symptoms of pain and abnormal pancreatic function are observed. These symptoms occur after the adenocarcinoma has advanced significantly, making PDAC more resistant to current therapies than other cancer types (Schawkat et al., 2020).

Current Treatments

Surgery

Surgery, also called resection, has been used to treat PDAC since 1882, but the standard procedures of resection have been steadily evolving since then. In 1898, the first pancreaticoduodenectomy was performed. Within this procedure, the head of the pancreas and part of the duodenum is removed. This procedure was later refined by Allen O. Whipple during the 20th century. The Whipple procedure is the current standard of PDAC resection (Fingerhut et al., 2018). Resection is the first course of action post-diagnosis should the patient be eligible because resection removes part or all of the tumor (Principe et al., 2021). Candidacy for resection is dependent on arterial contact and the extent of metastasis if metastasis has occurred, but, because PDAC is typically diagnosed at a stage that is considered unresectable, only 15-20% of patients qualify for resection. The standards for resection candidacy are evolving, though, because of breakthroughs wherein neoadjuvant (before surgery) therapies are rendering previously unresectable tumors resectable. PDAC patients who undergo resection with adjuvant chemotherapy have a 5-year survival rate of 30% as opposed to 3% for those that do not undergo resection. Therefore, resection with adjuvant therapy produces the greatest 5-year survival rate of any treatment and should be utilized whenever possible (Strobel et al., 2019).

Chemotherapy

Chemotherapy has existed since the early 20th century but was not originally used to treat cancer. It was discovered during World War II that mustard gas reduced white blood cell count which led researchers to investigate the effects of mustard gas ingredients on cancer: starting with lymphoma. Nitrogen mustard (a less volatile mustard gas derivative) was effective in reducing lymphatic tumor size. Cytotoxic (cell-killing) agents which we now call chemotherapy have been used to kill cancer ever since (De Vita et al., 2008).

Chemotherapy works by attacking cancer cells during division and reaches every part of the body through the circulatory system, so chemotherapy is a favorable treatment option for attacking cancer cells that cannot be removed via resection or for reducing tumor size before resection (Amjad et al., 2023). Chemotherapy is a treatment used for the vast majority of intent-to-treat PDAC patients - both resectable and unresectable. (Principe et al., 2021) There is a variety of chemotherapy drugs used to treat PDAC, including 5-Fluorouracil, Oxaliplatin, Albumin-bound paclitaxel (Abraxane), Capecitabine (an oral 5-FU drug), Cisplatin, Irinotecan, and Gemcitabine. These drugs are used in combination to make treatment more effective should the patient be healthy enough to endure more than one drug at once (American Cancer Society, 2020). FOLFIRINOX or GA are the most common drug combinations used to treat PDAC (Klein-Brill et al., 2022).

Chemotherapy is currently the most effective PDAC treatment available, especially when combined with neoadjuvant or adjuvant therapy, and is, therefore, a first-line treatment. However, resistance to chemotherapy is common and grows more frequent as the time a patient is administered chemotherapy increases. Resistance to chemotherapy, the inability to undergo chemotherapy, or the decision of the patient are the only major reasons treatments other than chemotherapy are pursued. (Principe et al., 2021)

Chemotherapy Regimens

FOLFIRINOX has been the standard of PDAC treatment since it was discovered in 2010 that FOLFIRINOX is superior to gemcitabine in terms of survival rate (Williet et al., 2019). Fluorouracil, leucovorin, irinotecan, and oxaliplatin are drugs used in FOLFIRINOX (Perri et al., 2020). FOLFIRINOX is administered intravenously through cycles, as shown in Figure 3. The number of cycles is dependent on the patient's specific needs (Cancer Research UK, 2021). FOLFIRINOX may be used neoadjuvant or adjuvant and improves survival and resection rate in both scenarios (Perri et al., 2020) (Klaiber et al., 2020). FOLFIRINOX is, however, often accompanied by severe side effects which reduce the amount of PDAC patients that are healthy enough to undergo the treatment due to comorbidities (Williet et al., 2019).

FOLFIRINOX Treatment Cycle
Day 1
oxaliplatin as a drip for over 2 hours
folinic acid as a drip for over 2 hours
irinotecan as a drip for 60 to 90 minutes
fluorouracil as an injection for 5 minutes (dependent on the individual patient)
fluorouracil as an infusion over 46 hours given by a small portable pump.
Day 2
fluorouracil as an infusion given by a small portable pump.
Day 3 to 14
no treatment.

Gemcitabine Plus Nab-Paclitaxel Treatment Cycle
Day 1
30 minutes nab-paclitaxel drip
30 minutes gemcitabine drip
Day 8
30 minutes nab-paclitaxel drip
30 minutes gemcitabine drip
Day 15
30 minutes nab-paclitaxel drip
30 minutes gemcitabine drip
Day 28
Rest and cycle restarts

Figure 3. The treatment cycles of Folfirinox and Gemcitabine plus Nab-Paclitaxel are shown. Both chemotherapy treatments are administered intravenously. FOLFIRINOX is a combination of 5 drugs, requiring more time to administer than Gemcitabine plus Nab-Paclitaxel. The typical cycle length of FOLFIRINOX is 14 days and 28 days for Gemcitabine plus Nab-Paclitaxel. Each cycle is subject to change depending on the needs of each patient.

GA has been used to treat PDAC since 1996 and is a first-line treatment for patients unable to undergo FOLFIRINOX because of comorbidities or cost. GA is composed of gemcitabine plus nanoparticle albumin-bound (nab)–paclitaxel and is administered intravenously and cyclically. The side effects of GA are mild compared to FOLFIRINOX, but the survival rate of GA is less (Williet et. al., 2019)(Perri et. al., 2020).

Immunotherapy

The concept of the immune system and immunotherapy has existed since ancient Greece, but immunotherapy was not integrated into oncology until the 19th century when Dr. William Coley used a bacterial infection to treat sarcomas (Eno, 2017). Immunotherapy works by using a patient's immune system (T cells) against cancer (American Cancer Society, 2019). The types of immunotherapy used to fight PDAC are immunomodulators, oncolytic viruses, adoptive cell therapies, and cancer vaccines (Timmer et al., 2021). Immunotherapy has proven to be ineffective compared to chemotherapy and resection in terms of recurrence-free survival rate but is helpful when resistance to chemotherapy is present. (Rémond et al., 2022)

Immunomodulators

Immunomodulators may be subdivided into three categories: immune checkpoint inhibitors, immune stimulatory agonists, cytokines, and bispecific antibodies (Timmer et al., 2021). Immune checkpoint inhibitors work by preventing proteins found in immune cells, such as T cells, from binding together. Because bound proteins called checkpoints keep T cells from killing cancer cells, immune checkpoint inhibitors are efficient at killing cancer via T cells attacking cancer cells (National Cancer Institute, 2022). Immune stimulatory agonists activate innate immune cells as well as T cells. Immune stimulatory agonists make the immune system more effective against cancer cells than T cells alone (Cancer Research Institute, 2023). Cytokines are used to communicate with cancer cells and give instruction contrary to the current operation (Conlon et al., 2019). Bispecific antibodies bind to two antigens (proteins found in cancer cells) simultaneously and redirect the function of the immune system to become immune to specific types of antigens (Ordoñez-Reyes et al., 2022)(National Cancer Institute, 2023).

Oncolytic Viruses

An oncolytic virus genetically modifies immune response which affects how the patient responds to cancer. This modified response may include killing cancer cells directly or decreasing blood circulation to the tumor which kills cells indirectly. Oncolytic viruses are ineffective compared to other treatments because PDAC tumors do not express neoantigens, making them less visible to the immune system and therefore inhospitable for the replication of the virus or invisible to the immune system post-infection (Haller et al., 2020).

Adoptive Cell Therapies

Adoptive cell therapies work by extracting, modifying, and re-infusing T cells. Adoptive cell therapies are typically administered to patients that do not have fully functioning T cells or have T cells that fail to recognize the tumor (naïve). The purpose of adoptive cell therapy is to increase the number of T cells and make them more effective which allows for a more effective immune response against cancer cells (Cancer Research Institute, 2023).

Vaccines

There are three major vaccines used for PDAC treatment: dendritic cell-based (DC), tumor cell-based, and bacterium-based (Fan et al., 2020)(Fig. 4). Dendritic cell vaccines "educate" dendritic cells by alerting them to the presence of antigens. Dendritic cells, once educated, attack antigens, thus killing cancer cells (Calmeiro et al., 2020).

Tumor cell-based vaccines may be classified as allogeneic or autologous depending on where biological matter used in the creation of the vaccine is sourced. Allogeneic vaccines come from biological material sourced from somewhere other than the body of the host whereas autologous vaccines use biological material sourced from within the body. Allogeneic vaccines are made from lab-grown cancer cells. This approach is inferior to that of analogous vaccines in that "patient-specific" tumor antigens are used which makes the vaccine less effective against each patient's specific antigens. The advantages of allogeneic vaccines are a low production cost and a relatively noninvasive procedure. Autologous vaccines require the extraction of tumor cells through an invasive procedure (resection). The problem with autologous vaccines is that there are different types of cancer cells within each tumor, so to kill every type, a sample of every type must be taken. Therefore, the efficacy of an autologous vaccine depends greatly on the volume of the sample. This is problematic because, in any scenario wherein a cancer vaccine would be used, resection would have been previously deemed impossible due to the risk posed to the patient, so a large-volume sample would be impossible to obtain. Because resection is necessary to create an analogous vaccine, analogous vaccines are inherently ineffective as a stand-alone treatment because certain types of tumor cells will inevitably be unaddressed by the vaccine and therefore continue to spread (Srivatsan et al., 2014).

Bacterium-based vaccination for PDAC is limited to the use of Listeria monocytogenes, a food-borne pathogen. In a Phase I clinical study, Listeria monocytogenes, once modified to be less toxic and further express mesothelin, produced a survival rate of 15 months for 37% of patients (Salman et al., 2013). Bacterium-based cancer vaccination results in side effects much milder than most cancer treatments (Gupta et al., 2021).

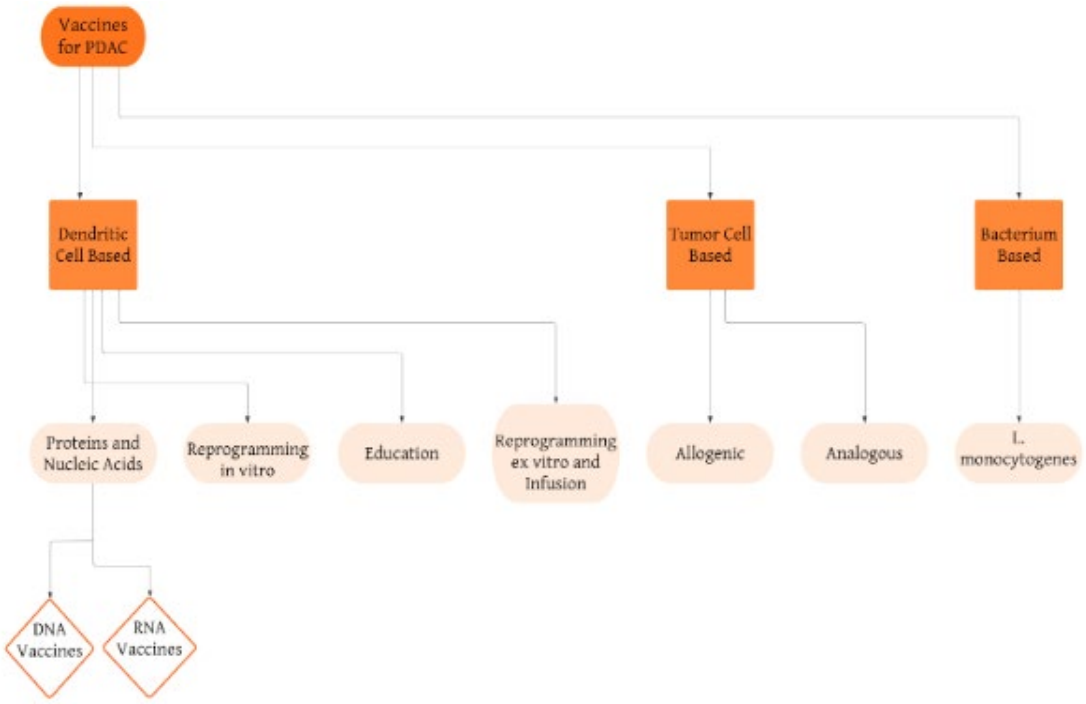

Figure 4. A flow chart of PDAC immunotherapy treatments is shown. Each type of immunotherapy belongs to the group above it which is connected by a line.

Radiotherapy

The discovery of X-rays was announced on January 26, 1896. X-rays were used to treat breast cancer just three days later, thus radiotherapy entered clinical practice (Huh et al., 2020). Radiation therapy has been used to treat PDAC for decades, but its efficacy is now a controversial topic and is rarely implemented to treat PDAC. The current practice of radiation therapy is to make localized ablations on tumors. These ablations may be incurred neoadjuvant or adjuvant. Because the only potentially curative treatment for PDAC involves resection of the largest part of the tumor, chemotherapy for the majority of what is left, and radiation therapy for microscopic tumor fragments that chemotherapy missed, radiation therapy is an integral part of PDAC treatment. Radiation therapy is not only useful in the context of chemotherapy but also in rendering previously unresectable tumors resectable by killing locally advanced regions of the tumor and preventing metastasis (Hall et al., 2021).

Treatments in Clinical Trials

Cediranib plus Olaparib

Cediranib maleate prevents the growth of blood vessels in tumors. Impeded circulation to the tumor leads to the death of cancer cells because of a lack of oxygen (UCSF, 2023). Olaparib is a protein inhibitor that is currently used to maintain the state of advanced tumors by inhibiting certain proteins and enzymes necessary for the spread of cancer. Olaparib may enhance the efficacy of chemotherapy and reduce chemotherapy resistance (NCI, 2023). The goal of a Phase II study by UCSF is to “determine the objective response rate” of cediranib maleate plus olaparib and the safety thereof in patients with metastatic or advanced tumors (UCSF, 2023).

Gemcitabine Hydrochloride With or Without Erlotinib Hydrochloride Followed by the Same Chemotherapy Regimen With or Without Radiation Therapy and Capecitabine or Fluorouracil in Treating Patients With Pancreatic Cancer That Has Been Removed by Surgery

Gemcitabine hydrochloride, as previously discussed, is a chemotherapy drug and, therefore, kills cancer cells directly (NCI, 2023). Erlonitib inhibits abnormal protein production (NCI, 2023). Capecitabine is converted to fluorouracil in the body (NCI, 2023). Fluorouracil is a chemotherapy drug (Cancer Research Institute, 2022). The main goal of this Phase III trial is to determine what combination of the current standard of adjuvant therapy plus radiation and or Fluorouracil or capecitabine produces the greatest survival indicators. A secondary goal of the study is to observe the side effects of each combination of adjuvant treatments and evaluate their respective efficacies (NCI, 2023).

Study of Covalent Menin Inhibitor BMF-219 in Adult Patients With KRAS Driven Non-Small Cell Lung Cancer, Pancreatic Cancer, and Colorectal Cancer

A menin inhibitor works by preventing the production of proteins necessary to create the target genes that eventually cause cancer (NHI, 2023). A menin inhibitor that is covalent shares bonds with problematic proteins and interacts along with them to prevent abnormal function (Huanrong et al., 2014-2022). The goal of the Phase I study is to determine the safety and efficacy of the covalent menin inhibitor BMF-219 in patients with PDAC, NSCLC, or CRC (UCSD, 2023).

The Future of PDAC Treatment

Because the current state of PDAC treatment is so dismal, with cases increasing as well as the mortality rate, "success" in the future treatment of PDAC may be characterized by a smaller delta than that of other cancers (Siegel et al., 2020). The advances in recent years, specifically in the domain of personalized immunotherapy, have set a precedent for improvement in the RFS of chemotherapy-resistant PDAC patients (Rémond et al., 2022). Chemotherapy is currently the most effective stand-alone treatment for PDAC, but new drug combinations with expected RFS increases are under clinical trials (UCSF, 2023). As previously mentioned, the reasons that PDAC is so difficult to treat and cure are multifaceted, but the main cause is that PDAC is detected at stage II or later - a stage when considerable advancement has already taken place. The key to curing and treating PDAC may very well be prevention and earlier detection via medical imaging (Schawkat et al., 2020). Though mass screening for PDAC in average to low-risk individuals is not feasible and does not show an increased survival rate, preventative screening for high-risk individuals has proven effective in increasing survival rate. The main challenge faced in early detection of PDAC is the identification of biomarkers. Other than family genetic history and previous pancreatic dysfunction, there is no isolated common factor (not exhibited by the general population) that determines the probability of PDAC. However, new imaging strategies are emerging. CT and MRI are the current standards of PDAC imaging, but ES (endoscopic ultrasound) is proving to be more effective in diagnosing PDAC when combined with FNA (fine needle aspiration) which extracts fluid that is then analyzed for chemical biomarkers of PDAC (Singhi et al., 2019).

The emergence of future therapies and effective utilization of current therapies give PDAC treatment a bright future. Both therapies and imaging procedures are becoming more advanced and tailored to each patient. It is through personalized medicine that maximum efficacy and minimum toxicity may be achieved, thus decreasing mortality rates and improving the life of each PDAC patient (O'Kane et al., 2022).

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