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# Pancreatic Cancer Treatment

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## Abstract

Pancreatic cancer is one of the most aggressive and lethal human cancers, with more than 200, 000 deaths worldwide every year. Despite recent efforts, conventional treatment approaches, such as surgery, classic chemotherapy, radiotherapy, biologic therapy and palliative care have only slightly improved patient outcomes. Among the conventional chemotherapies the combination of abraxane (*nab*-paclitaxel) with gemcitabine and FOLFIRINOX (5-FU/leucovorin, irinotecan, and oxaliplatin) with gemcitabine in metastatic pancreatic cancer patients are promising. Among the targeted therapies the combination of gemcitabine, erlotinib and capecitabine are likely to form the base for future treatment. Under biologic or immunotherapy KRAS-targeting vaccines, telomerase-targeting vaccine (GV1001), gastrin-based vaccine, dendritic cell (DC)-based vaccine alone or combined with lymphokine-activated killer (LAK) cells and allogeneic GM-CSF-secreting vaccine (GVAX) are well tolerated by patients and could represent a new therapeutic option for pancreatic cancer. Moreover a novel strategy for using mesenchymal stem cells (MSCs) as means of delivering anticancer genes to the site of pancreas is also encouraging. Current and future clinical trials using natural compounds such as vitamin E compound delta-tocotrienol and curcumin in combination with standard chemotherapy are ongoing to discover more effective ways of treating advanced pancreatic cancer.

**Keywords:** Pancreatic cancer; Surgery; Chemotherapy; Clinical trials; Treatment

## Introduction

Pancreatic cancer is an aggressive and highly lethal form of pancreatic malignancy [1]. The incidence of pancreatic cancer varies greatly across regions, with the highest incidence and mortality rates found in developed countries. Over 2 million people die annually due to pancreatic cancer worldwide with an increasing incidence. Deaths from pancreatic cancer rank fourth among cancer-related deaths in the United States and it is one of the common gastrointestinal malignancies [2]. Risk factors for pancreatic cancer include, among others, high-fat diet, smoking, chronic pancreatitis, primary sclerosing cholangitis, hereditary pancreatitis, family history of pancreatic cancer, and diabetes mellitus [3]. Age seems to be a significant risk factor, with incidence increasing with age. It possesses some characteristics, such as fast progress, high degree of malignancy and early metastasis, which eventually bring poor prognosis for patients with a 5-year survival rate of only l% to 3% [4]. Approximately 20% of patients present with localized, potentially curable tumors. The majority (95%) of cases of pancreatic cancer are adenocarcinomas, resembling the pancreatic ductal cell. Metastasis of this cancer can be either local, most often involving the liver, lung, spleen, lymphatic system, adrenal glands and transverse colon [5].

Despite recent progress in understanding the multistep progression from precursor lesions to cancer, pancreatic ductal adenocarcinoma is still detected too late when cure is impossible justifying the significant need to develop novel early detection, prevention, and treatment strategies. Pancreatic carcinogenesis is a multistep process that involves the accumulation of a set of genetic changes that convert normal cells first to premalignant cells and then to malignant cells [6,7]. In a recent study, an average of 63 mutations per cancer was altered in 24 human pancreatic ductal adenocarcinomas [8]. The most widely accepted explanation for the accumulation of multiple mutations in the same cell is the model of clonal evolution when cells with one crucial mutation expand clonally [9]. By increasing in number through mitosis and suppression of apoptosis, cells with the first mutation become more likely to develop a second mutation, which predisposes to a third mutation and so on. Continuing clonal expansion, selection, and heterogeneity allow the accumulation of multiple mutations in the same cell and the ultimate generation of malignant clones. Therefore, reducing the number of premalignant cells or eliminating them altogether should be a potent way to reduce pancreatic cancer risk [10]. Pancreatic carcinogenesis requires silencing of proapoptotic genes and activation of antiapoptotic genes to circumvent apoptosis of premalignant cells, which is the physiological fail-safe mechanism to eliminate transformed cells [11-13]. No chemoprevention agent exists for pancreatic cancer and less than 5 agents have entered early phase clinical investigation [14]. Cancer chemoprevention uses natural, synthetic, or biological agents to reverse, suppress, prevent, or delay either the initial phase of carcinogenesis, or the progression of premalignant cells to cancer [15]. The concept of eliminating premalignant cells periodically has been proposed recently as a novel intermittent approach for cancer prevention [10]. A potential advantage of this approach is the prospect of less toxicity and increased compliance due to the need for brief intermittent therapy instead of continuous therapy. This review focuses the current and future pancreatic cancer treatment modalities as well as on going clinical trials in the clinic. Pancreatic cancer is treated in several ways, alone or in combination based upon the stages of the malignancy:

- Surgery
- Chemotherapy
- Radiation therapy

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- Biologic therapy
- Palliative care

## Surgery

Currently, surgery is still the most basic means for treating pancreatic cancer, also the only method of hoping for curative treatment. Since the first successful implementation of surgery in 1935 by Whipple procedure in which the tumor-bearing region of the pancreas along with a portion of stomach, duodenum, gallbladder, and part of bile duct are removed and the remaining regions are reattached to support digestive capabilities of the patient [16], pancreatoduodenectomy (PD) has been the standard operation for pancreatic cancer [17]. As pancreatic cancer spreads to regional lymph nodes and even to the pancreas plexus along the perineurium, efforts to improve the surgical method have been based on conventional PD and variations of extended PD, such as pancreatoduodenectomy with extended lymphadenectomy (PD/ELND) [18]. Despite the fact that surgical options for pancreatic cancer are now associated with acceptable outcomes, they often prove ineffective in controlling the disease with reported recurrence rates approaching almost 80% (both locally and distant) and a 5-year survival rate of only 10–24% for cases involving total resection [19]. Lack of distant metastasis and local vascular invasion are the two criteria that must be present to qualify for a curative resection [16]. The study concluded that PD/ELND fails to gain advantages over standard PD in the survival rate of patients with pancreatic cancer, but may increase the operative time and the incidence of postoperative complications [18]. Currently a phase III clinical trial is underway at NCI utilizing pancreas resection with and without drains (NCT01441492). Chemotherapy and radiation are often given together, prior to, after, or even without surgery, to slow pancreatic cancer's growth.

## Chemotherapy/Radiotherapy/Biologic therapy

Other treatment options range from systemic chemotherapy alone to combined forms of treatment with chemoradiation and chemotherapy. Chemotherapy treatments can be categorized as adjuvant (treatment after surgery), neo-adjuvant (treatment prior to surgery), and palliative. The most common chemotherapy drugs used to treat pancreatic cancer are the following: gemcitabine, 5-fluouracil, capecitabine, cisplatin, and oxaliplatin [20]. These drugs function on the basis of cross-linking mechanisms in which their reactive region interacts with the cell's DNA or RNA nucleotides, thus disrupting the cell cycle progression leading to cancer cell apoptosis [21,22]. Chemoradiotherapy is an efficient therapeutic approach for pancreatic cancer patients; however, there are no data to support a radiotherapy alone treatment option [22]. A phase II clinical trial using short course radiation therapy with proton beam capecitabine and hydroxy chloroquine for resectable pancreatic cancer is underway at NCI (NCT01494155). Due to poor treatment options for pancreatic cancer patients, new therapeutic strategies are being developed using anticancer gene therapy agents and treatments as an alternative solution or in combination to the existing treatments. These strategies can be categorized as either using RNA interference or antisense oligonucleotides that inhibits the activated oncogenes (Kirsten rat sarcoma (KRAS), LSM1, Akt, and Wnt) or approaches to restore function of the tumor suppressor genes (p53, p16/ CDKN2A, DPC4/ SMAD4) [23]. For over a decade, gemcitabine-based therapy has been considered a first-line treatment for locally advanced and metastatic pancreatic cancer. Preference for gemcitabine over 5-fluorouracil (5-FU) was established, when comparing gemcitabine monotherapy to 5-FU demonstrated clinical benefit in gemcitabine-treated patients with advanced pancreatic cancer [5]. The value of radiotherapy in the management of locally advanced pancreatic cancer remains unclear. Several clinical trials were undertaken with gemcitabine in combination with 5-FU, irinotecan, oxaliplatin, pemetrexed, exatecan and cisplatin [24,25], all failed to show superiority over gemcitabine monotherapy. Capecitabine is an orally administered fluoropyrimidine that is metabolized in both liver and tumor cells into 5-FU, resulting in high intratumoral 5-FU concentrations. Clinical trial on capecitabine and gemcitabine combination showed significantly improved objective response rate and progression-free survival, but did not show superiority in overall survival in patients with advanced pancreatic cancer [26]. In addition, folfirinox (5-FU/leucovorin, irinotecan, and oxaliplatin) treatment of metastatic pancreatic cancer patients in a randomized clinical trial of folfirinox versus gemcitabine indicated that response rate was more than 30%. Furthermore, the median overall survival was 11.1 months in the folfirinox group as compared with 6.8 months in the gemcitabine group, indicating that folfirinox is an option for the treatment of patients with metastatic pancreatic cancer [27].

Targeted therapies have also been tried for advanced pancreatic cancer. The matrix metalloproteinase inhibitors (MMPIs) marimastat and talomastat (BAY 12-9566) inhibit enzymes that play a key role in extracellular matrix (ECM) degradation, and angiogenesis. In clinical trial, neither marimastat monotherapy nor marimastat with gemcitabine improved overall survival compared with gemcitabine monotherapy [28]. The farnesyl transferase enzyme Kras regulator tipifarnib in combination with gemcitabine did not improve overall survival compared with gemcitabine monotherapy in a clinical trial [29]. Erlotinib is a small-molecule tyrosine kinase inhibitor of the human epidermal growth factor receptor (EGFR). A clinical trial of erlotinib in combination with gemcitabine, in patients with locally advanced or metastatic pancreatic adenocarcinoma met its primary endpoint, with the combination regimen being the first gemcitabine combination to demonstrate a statistically significant survival advantage over gemcitabine monotherapy and the regimen was consequently approved for metastatic disease [30]. Cetuximab, an anti-EGFR monoclonal antibody, blocks the extracellular EGFR domain, preventing ligand dependent or independent activation and downstream signaling. Unfortunately, it is failed to demonstrate a clinically significant advantage of the addition of cetuximab to gemcitabine for response and overall survival [31]. Bevacizumab is a recombinant, humanized IgG1 monoclonal antibody that selectively binds to vascular endothelial growth factor (VEGF), inhibiting its interaction with VEGF receptor-1 and -2, on the surface of endothelial cells. Despite recently reported negative results, clinical studies are underway in advanced pancreatic cancer that includes bevacizumab and cetuximab in combination with other agents [32]. Finally, a wide range of molecular-targeted agents that interact with crucial pathways for cell survival in pancreatic cancer are currently being explored. These include agents that target polyADP-ribose polymerase, histone deacetylase (HDAC), Src/Abl kinases, and mammalian target of rapamycin [33]. Given the positive data observed in clinical trials, gemcitabine, erlotinib and capecitabine are likely to form the base for future treatment strategies for advanced pancreatic cancer. Initial chemoradiotherapy is only used in specific circumstances such as up-front chemoradiotherapy is used in some patients with borderline resectable disease [34,35]. Mesenchymal stem cells (MSCs) have attracted significant attention in cancer research as a result of their accessibility, tumororiented homing capacity, and the feasibility of auto-transplantation [22]. A novel strategy for using MSCs as means of delivering anticancer genes to the site of pancreas is promising.

### Palliative care

Palliative treatment designed to control the symptoms of unresectable or recurrent pancreatic cancer can provide relief of pain, obstructive jaundice, gastric outlet obstruction, and pancreatic exocrine insufficiency. Furthermore, the incidence of venous thromboembolism is four- to sevenfold higher in patients with pancreatic cancer than in other common adenocarcinomas [36]. In addition, pancreatic cancer is one of the malignancies that are associated with a particularly high risk of depression. Up-front chemoradiotherapy is used in some patients and as palliative treatment in patients not deemed surgical candidates [37].

Options for palliation of jaundice in patients who have obstructive jaundice from locally advanced unresectable disease are surgical bypass or placement of a stent across the area of biliary tract obstruction. The surgical options for achieving biliary decompression include an anastomosis between the gallbladder and jejunum (cholecystojejunostomy) or common bile duct and jejunum (choledocho jejunostomy) [38]. Approximately 15 to 20 percent of patients with pancreatic cancer will develop duodenal obstruction leading to gastric outlet obstruction, although it is typically not present at diagnosis [38]. Endoscopically placed expandable metal stents are preferred over palliative gastrojejunostomy for patients with a symptomatic gastric outlet obstruction who are not undergoing an attempt at surgical resection. Early experience supports good symptom palliation and a lack of morbidity [39]. Up to 60 percent of patients with pancreatic cancer have slowed gastric emptying without evidence of gastro duodenal tumor invasion [40]. Unfortunately, vomiting is often difficult to control, although pro-kinetic agents such as metoclopramide may help [39]. Often, palliation of pain can be successfully achieved by opioid analgesics alone. For patients with persistent nausea and vomiting, for whom taking oral medications is difficult, pain, control may be achieved using transdermal patches. Pain can also be managed with celiac plexus neurolysis and radiation therapy [41]. As a general rule, 30,000 international units of pancreatic lipase, swallowed during each full meal, should suffice in reducing steatorrhea and preventing weight loss. Phase II trials of combination chemotherapies have shown encouraging palliative benefit, objective response rates, and survival outcomes [37]. Until ongoing phase III trials confirm these benefits, the current standard treatment for metastatic pancreatic adenocarcinoma remains single agent gemcitabine.

## Clinical Trials

Clinical trials are ongoing to discover more effective ways of treating pancreatic cancer. Recent clinical trial shows that the combination of abraxane (*nab*-paclitaxel) with gemcitabine in metastatic pancreatic cancer patients had the median survival (8.5 months) which was almost three months less than that of FOLFIRINOX (11.1 months) [42,43]. Another clinical trial showed the efficacies of the novel capecitabine and streptozocin+/-cisplatin regimens were very similar in pancreatic cancer. However CapStrep was better tolerated than Cap Strep Cis [44]. Other study suggests that a capecitabine-based regimen might be preferable to a gemcitabine-based regimen in the context of consolidation chemoradiotherapy after a course of induction chemotherapy for locally advanced pancreatic cancer [45]. In a second-line treatment for advanced pancreatic cancer the published clinical trials showed that patients who received treatments had a median overall survival of 6 months compared with 2.8 months for patients who received best supportive care only. The gemcitabine and platinum-based combination provided a median progression-free survival and overall survival of 4 and 6 months compared with 1.6 and 5.3 for the rest of the regimens and 2.9 and 5.7 for the combination of 5-fluorouracil and platinum agents [46]. Another clinical trial compared the long-term clinical efficacy of chemotherapy plus radiotherapy (CRT) with that of radiotherapy alone (RT) or chemotherapy alone (CT) for locally advanced pancreatic carcinoma (LAPC). Compared with CT or RT, CRT can benefit the long-term survival of LAPC patients, although it may also increase treatment-related toxicities [47]. The efficacy of nimotuzumab plus gemcitabine usage as first-line treatment in patients with advanced pancreatic cancer has also been reported [48]. Another Phase I/II study showed the efficacy of the natural compound curcumin when combined with gemcitabine in pancreatic cancer patients [49]. There are several phase I/II trials are being evaluated in pancreatic cancer patients using HDAC inhibitors in combination with chemo or radiation therapies such as SAHA [50], FK228 [50,51], VPA [51], 4-PB [52], CI-994 [53,54] and MGCD0103 [55]. Currently a phase II clinical trial is underway using the combination of irinotecan, oxaliplatin and cetuximab for locally advanced or metastatic pancreatic cancer at NCI (NCT00871169). A phase II clinical trial using cisplatin, metronomic low-dose interferon alfa, gemcitabine, and fever-range whole-body hyperthermia in treating patients with inoperable or metastatic pancreatic cancer is active at NCI (NCT00082862). A phase III clinical trial of 90Y-clivatuzumab tetraxetan and gemcitabine versus placebo and gemcitabine in metastatic pancreatic cancer is investigated at NCI (NCT01956812).

Under immunotherapy clinical trials patients with resected pancreatic cancers harboring **KRAS** mutations at codon 12 were vaccinated once monthly for 3 months. The median recurrence-free survival time was 8.6 months and median overall survival time was 20.3 months [56]. KRAS-targeting vaccines proved to be well tolerated by patients with resectable pancreatic cancer. The telomerase-targeting vaccine (GV1001) clinical study in non-resectable pancreatic cancer was well tolerated by the patients with prolonged survival. However recent phase III trial investigated the efficacy of GV1001 in sequential combination with gemcitabine versus gemcitabine alone in subjects with locally advanced and metastatic adenocarcinoma of the pancreas. The results demonstrated no survival benefit for the combination of GV1001 and gemcitabine as compared with gemcitabine alone [57]. In a multi-institutional, double-blinded, placebo-controlled clinical trial, the administration of a gastrin-based vaccine to chemotherapy-refractory advanced-stage cancer patients resulted in a nearly 2-fold increase in median overall survival, as compared with placebo [58]. Gastrin-based vaccines are well tolerated and could represent a new therapeutic option for pancreatic cancer. A dendritic cell (DC)-based vaccine alone or combined with lymphokine-activated killer (LAK) cells was administered together with gemcitabine to inoperable pancreatic cancer patients [59]. The median survival of these individuals was 360 d, which was longer than with gemcitabine. Thus, the combination of DC-based immunotherapy and chemotherapy was well tolerated by advanced pancreatic cancer patients and warrants further investigation. Allogeneic GM-CSF-secreting vaccine (GVAX) was tested in patients with metastatic pancreatic cancer under phase II trial along with cyclophosphamide. The median overall survival was 3.4 months [60]. A recent clinical study investigating the clinical profile of immune checkpoint inhibitor (ipilimumab) plus GVAX as compared with ipilimumab alone in previously treated locally advanced or metastatic pancreatic cancer patients [61]. The median overall survival in Ipilimumab alone was 3.3 months whereas median overall survival in Ipilimumab plus GVAX was 5.5 months. Currently a phase III clinical trial using gemcitabine with or without erlotinib 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 is underway at NCI (NCT01013649). Another phase I/II clinical trials using gemcitabine + nab-paclitaxel with LDE-225 (Hedgehog inhibitor) as neo-adjuvant therapy for pancreatic adenocarcinoma are active at NCI (NCT01431794). A phase II clinical trial using combination chemotherapy with or without oregovomab and stereotactic radiotherapy together with nelfinavir in treating patients with localized or locally advanced pancreatic cancer is going on at NCI (NCT01959672). Using natural plant products a phase I/II clinical trial are being evaluated in resectable pancreatic cancer patients using natural vitamin E compound delta-tocotrienol at NCI (NCT00985777). However ongoing phase I/II/III trials in patients with pancreatic cancer are needed to discover more effective ways of treating advanced pancreatic cancer.

## Conclusion

Over the last few years, the availability of a wide variety of different therapeutic agents and the ongoing clinical trails using combination of vaccines and standard chemotherapy proved patient outcomes. However, more sophisticated understanding of the biology of pancreatic cancer as well as deployment of more precise drugs combinations specifically vaccines predicts the effective treatment of this deadly malignancy.

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