Therapeutic Intervention of Human Pancreatic Cancer

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Abstract

Pancreatic cancer is one of the most lethal malignancies in the world. The incidence of pancreatic cancer keeps on increasing without a significant decrease in mortality. Current therapeutic options are surgical resections, radiation, and chemo, biologic, immune and palliative therapy. Surgical therapies are associated with acceptable outcomes but resected patients suffer from tumor recurrence. The role of post-operative radiotherapy reported increased survival. Currently four chemotherapy drugs approved by the United States Food and Drug Administration (US FDA) for the treatment of pancreatic cancer: ABRAXANE (albumin-bound paclitaxel), gemcitabine, 5-fluorouracil (5-FU) and ONIVYDE (irinotecan liposome injection). Among the conventional chemotherapies the combination of abraxane (nab-paclitaxel) with gemcitabine and FOLFIRINOX (5-FU/leucovorin, irinotecan, oxaliplatin) 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 antibodies against programmed death-1 receptor (PD-1), its ligand PD-L1, cytotoxic T lymphocyte associated antigen-4 (CTLA-4), KRAS-targeting vaccines, mucin-1 (MUC1) vaccine, 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 new therapeutic option for pancreatic cancer. Current and future clinical trials using natural compounds such as delta-tocotrienol, Huang-Qin-Tang (HQT) and its botanical formulation (PHY906) and curcumin in combination with other agents are ongoing to discover more effective ways of treating pancreatic cancer patients.

Keywords: Pancreatic cancer; Surgical therapy; Chemotherapy; Radiation therapy; Immunotherapy; Biologic therapy; Palliative therapy

Introduction

Pancreatic cancer is one of the most deadly malignancies both in men and women worldwide. It is one of the most common gastrointestinal cancers diagnosed and fourth leading causes of cancer related deaths in the United States [1,2]. More than 70% of the pancreatic cancer patients will die within the first year of diagnosis. Pancreatic cancer is predicted to be the second leading cause of cancer related mortality by 2030 [3]. Approximately 25% of patients with pancreatic cancer have localized disease that is amenable to a curative approach with surgical resection combined with adjuvant chemotherapy [4,5]. However, the prognosis of these patients remains poor, with a 5-year overall survival rate of only 23.4% [6,7]. The poor prognosis is mainly attributed by the lack of specific symptoms and biomarkers for early diagnosis, aggressive metastatic spread that is resistant to chemotherapy [8,9]. The majority of cases of pancreatic cancer are Pancreatic Ductal Adenocarcinoma (PDAC). Metastatic spread of PDAC involves liver, lung, spleen, lymphatic system, adrenal glands and transverse colon [10]. There is an urgent need to develop chemoprevention and therapeutic agents that can prevent pancreatic cancer progression and metastatic spread.

Cancer chemoprevention/treatment involves natural/synthetic or biological agents to reverse/suppress/prevent, or delay carcinogenesis, or the progression of premalignant cells to tumor [11]. Chemotherapeutics for the treatment of advanced pancreatic cancer involves targeting multiple signaling molecules with combinations of individual drugs, use of drugs that target multiple signaling molecules and combinations of vaccines with immuno-modulatory drugs. This review focuses the current and future pancreatic cancer treatment modalities as well as ongoing clinical trials in the clinic. Pancreatic cancer patients are treated in several ways, alone or in combination

based upon the stages of the malignancy:

- Surgical Therapy
- Radiation Therapy
- Chemotherapy
- Biologic Therapy
- Immunotherapy
- Palliative Therapy

Surgical Therapy

Surgery is one of the most basic methods for curative treatment of pancreatic cancer. The surgical options for pancreatic cancer are: pancreaticoduodenectomy (head/body of the pancreas and nearby organs is removed), distal pancreatectomy (tail, body and spleen), and total pancreatectomy (whole pancreas and nearby organs). The Whipple Procedure, or Pancreaticoduodenectomy (PD), is the most commonly performed surgery to remove tumors in the pancreas. It is currently a safe procedure and results in low mortality and morbidity [12]. When pancreatic cancer spreads to regional lymph nodes, then conventional PD and variations of extended PD, such as PD with extended lymphadenectomy (PD/ELND) are used [13]. During the last few decades the chance of survival for surgical patients has significantly increased and the mortality rates do not exceed 5% [14]. Although surgical options for pancreatic cancer are now associated with acceptable outcomes. However, majority of resected patients suffers from tumor recurrence (80%, both locally and distant) and a 5-year survival rate of only 10% to 24% for cases involving total resection [15,16]. Therefore, the necessity for preoperative and postoperative therapies is needed in order to achieve more effective treatments. Currently a phase III clinical trial is underway at NCI utilizing pancreas resection with and without drains (NCT01441492).

Radiation Therapy

Radiation therapy is another option for locally unresectable pancreatic cancer. Radiation therapy may be given alone or in combination with chemotherapy. When chemotherapy is given in combination with radiation, usually a low dose of chemotherapy is used [17]. There are two main types of radiation therapy, external beam radiation therapy and internal radiation therapy. External beam radiation therapy is commonly used in treating pancreatic cancer patients. Intensity-Modulated Radiation Therapy (IMRT) is a type of external beam radiation therapy that delivers focused radiation to the tumor by modulating the intensity of the radiation beam under precise computer control. Stereotactic Body Radiation Therapy (SBRT) is a type of external beam radiation therapy designed to deliver high doses of radiation precisely to small tumors, usually in five or fewer treatments. Cyber Knife is one type of SBRT commonly used. Proton beam radiation therapy is a type of external beam radiation therapy that uses proton beams rather than x-rays. It is generally causes fewer side effects and being studied in clinical trials for pancreatic cancer. Modern radiation techniques such as Image-Guided Radiotherapy (IGRT) and Intensity-Modulated Radiotherapy (IMRT) are effective for patients with locally advanced pancreatic cancer after prolonged pre-radiation chemotherapy [18,19]. A positive role of post-operative radiotherapy was confirmed by a large retrospective analysis [20] which identified radiotherapy in addition to adjuvant chemotherapy as a favorable prognostic indicator for survival. A phase II clinical trial using short course radiation therapy with proton beam capecitabine

and hydroxychloroquine for resectable pancreatic cancer is underway at NCI (NCT01494155).

Chemotherapy

Chemotherapy treatments can be categorized as adjuvant (treatment after surgery), neo-adjuvant (treatment prior to surgery), and palliative. There are currently four chemotherapy drugs approved by the united states Food and Drug Administration (FDA) for the treatment of pancreatic cancer: ABRAXANE (albumin-bound paclitaxel), gemcitabine, 5-fluorouracil (5-FU) and ONIVYDE (irinotecan liposome injection). Gemcitabine was approved in 1996 for the treatment of unresectable pancreatic cancer. Studies have also shown that there is a benefit to using gemcitabine after surgery (adjuvant therapy) [21]. Prior to gemcitabine, 5-FU was used as the standard treatment for unresectable pancreatic cancer. ABRAXANE was approved to be used in combination with gemcitabine as first-line treatment for metastatic pancreatic in 2013 [22,23]. ONIVYDE in combination with 5-FU and leucovorin was approved in 2015 as treatment for metastatic pancreatic cancer that has progressed following treatment with gemcitabine based therapy [24]. In addition to above FDA-approved drugs, FOLFIRINOX (5-FU/leucovorin, irinotecan, oxaliplatin) is commonly used in the treatment of metastatic pancreatic cancer. A Phase III clinical trial showed positive results for patients treated with FOLFIRINOX [25]. Due to the results of this study, FOLFIRINOX is also considered a standard treatment option for patients with metastatic pancreatic cancer. Targeted therapies have also been tried for advanced pancreatic cancer. In 2005 FDA approved the targeted therapy drug erlotinib in combination with gemcitabine for use in advanced pancreatic cancer that cannot be removed by surgery. The regimen was consequently approved for metastatic pancreatic cancer [26]. In 2011 FDA approved two targeted therapy drugs, sunitinib and everolimus for the treatment of advanced pancreatic neuroendocrine tumors [27]. 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]. 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 [30]. 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 include bevacizumab and cetuximab in combination with other agents [31]. 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 [32]. Initial chemoradiotherapy is only used in specific circumstances such as up-front chemoradiotherapy is used in some patients with borderline resectable disease [33,34]. Other treatment strategies are either using RNA interference or antisense

oligonucleotides that inhibits the activated oncogenes (Kirsten rat sarcoma (KRAS), LSM1, Akt, Wnt) or approaches to restore function of the tumor suppressor genes (p53, p16/ CDKN2A, DPC4/SMAD4) [35-37].

Biologic Therapy

Several natural biological compounds have shown antitumor activity against different types of cancer including pancreatic cancer [38]. Curcumin is a natural compound isolated from the rhizome of Curcuma longa. Phase I clinical trials with curcumin have shown that curcumin is relatively safe, even at high doses in humans. However, curcumin has limited bioavailability because of poor absorption, rapid metabolism, and rapid systemic elimination [39]. Phase I/II clinical trials in patients with gemcitabine-resistant pancreatic cancer showed that oral administration of curcumin resulted in an increased median survival time and a one-year survival rate of 19% [40,41]. The Curcumin Analogue Difluorinated-curcumin (CDF) showed better bioavailability and 10-fold higher concentrations in the pancreas compared with curcumin [42]. Repetitive systemic exposure to high concentrations of Theracurminr, a new form of curcumin developed to increase bioavailability, did not increase the incidence of adverse events in patients with cancer who were receiving gemcitabine-based chemotherapy [43]. Natural vitamin E delta-tocotrienol has shown antitumor activity in different types of cancer including pancreatic cancer in preclinical models [44-47]. In clinical trial study phase I delta-tocotrienol at doses (200 mg to 1600 mg) daily taken orally for 2 weeks before pancreatic surgery was well tolerated, reached bioactive levels in blood, and significantly induced apoptosis in the neoplastic cells of patients with pancreatic ductal neoplasia [48]. Ginkgo biloba extract GBE 761 ONC combined with 5-FU was shown effective to treat pancreatic cancer patients in the clinical trial phase II study, compared to the clinical trial of 5-FU monotherapy [49]. Natural Mistletoe extracts from the medicinal herb Viscum album L was used as supportive care in an adjuvant chemotherapy setting with gemcitabine or 5-FU in patients undergoing curative intent resection of pancreatic cancer [50]. In clinical trial phase Ib study of patients with inoperable pancreatic carcinoma treated with gemcitabine and AXP107-11(sodium salt dihydrate form of genistein) led to a favorable pharmacokinetics with high serum levels without toxicity [51]. Traditional Chinese herbal formulation Huang-Qin-Tang (HQT), Botanical formulation PHY906, a, A phase I/II study of PHY906 (pharmaceutical grade of Chinese Huang-Qin-Tang) in combination with capecitabine showed a feasible and safe salvage therapy after the failure of gemcitabine for advanced pancreatic cancer [52,53]. Mesenchymal Stem Cells (MSCs) have attracted significant attention in cancer research as a result of their accessibility; tumor oriented homing capacity, and the feasibility of auto-transplantation [54]. A novel strategy for using MSCs as means of delivering anticancer genes to the site of pancreas is promising.

Immunotherapy

Induction of an anti-tumor immune response has been demonstrated to be effective in different types of advanced malignancies including pancreatic cancer. Recent attempts have been made to regulate the responses of various immune modulatory cells by targeting their signaling molecules: Programmed Death-1receptor (PD-1) as well as its ligand PD-L1, Cytotoxic T Lymphocyte Associatedantigen-4 (CTLA-4), Dipeptidyl Peptidase-IV (DPP-IV), CD40, and mucin1 (MUC1) [27,37]. Antibodies targeting PD-1 receptor or PD-L1 are being investigated [55]. Phase I/II trials examining antibodies targeting CTLA-4 (Ipilimumab) are ongoing [56] (NCT01928394). Nivolumab (anti-PD-1 antibody) alone or in combination with ipilimumab, gemcitabine or other antibodies (NCT01473940 NCT02423954, NCT02526017, NCT02381314) are currently being tested. Studies of another anti PD-1 antibody, pembrolizumab (NCT02268825, NCT02305186) alone or in combination with gemcitabine and FAK inhibitor defactinib (NCT02546531), are also ongoing. Another combination of anti-PDL1 and anti-CTLA4 antibodies (Durvalumab and Tremelimumab respectively (NCT02558894, NCT02639026, NT02311361, NCT02527434) or durvalumab with mogamulizumab-anti-CCR4 antibody (NCT02301130) is being investigated in patients with advanced pancreatic cancer. A phase I/II study testing the combination of ulocuplumab (anti-CXCR4) and nivolumab (anti–PD-1) in PDAC is in progress (NCT02472977). A Phase Ib/II trial of gemcitabine/nab-paclitaxel combined with indoximod (inhibitor of indoleamine-2, 3-dioxygenase) showed moderate and sustained activity [27]. Talabostat, a competitive inhibitor of DPP-IV, is being investigated in metastatic pancreatic cancer [57] (NCT00116389). A combination of a monoclonal antibody (CP-870,893) against CD40 with gemcitabine induced a measurable anti-tumor immune response in clinical trials [58,59]. The Japanese Kampo medicine Juzen-Taihoto/TJ-48 administration to patients with advanced pancreatic cancer significantly decreased Foxp3(+) Treg populations and increased the CD4/CD8 ratio [60]. A phase III clinical trial of 90Y-clivatuzumab tetraxetan and gemcitabine versus placebo and gemcitabine in metastatic pancreatic cancer is investigated at NCI (NCT01956812). Another phase I/II clinical trials using gemcitabine + nab-paclitaxel with LDE-225 (Hedgehog inhibitor) as neoadjuvant 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). However ongoing phase I/II/III trials in patients with pancreatic cancer are needed to discover more effective ways of treating advanced pancreatic cancer.

Vaccine-based therapies are designed to enhance the immune system response against tumor-associated antigens. Immune responses to mucin-1 (MUC1) vaccine have been tested in clinical studies with adjuvant therapy [61,62]. In a clinical trial phase I/II study of a MUC1 peptide-pulsed autologous dendritic cell vaccine as adjuvant therapy in patients with resected pancreatic tumor the survival was increased [63]. The Telomerase-Targeting Vaccine (GV1001) or PANVAC-V was studies in non-resectable pancreatic cancer which was well tolerated by the patients with prolonged survival [64]. 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 demonstrated no survival benefit for the combination of GV1001 and gemcitabine as compared with gemcitabine alone [65,66]. 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 showed increased median survival than gemcitabine alone [67]. Several vaccine-based combinations clinical trials are currently ongoing (e.g., ipilimumab ± vaccine therapy GVAX Pancreas vaccine (designed to secrete GM-CSF) ± nivolumab, GVAX, CRS-207 (vaccine targeting mesothelin protein) ± nivolumab or HyperAcute Pancreas

(algenpantucel-L) for resectable and metastatic pancreatic cancers [27,68] (NCT02243371, NCT02405585).

Palliative Therapy

Palliative treatment is employed to control the symptoms of unresectable or recurrent pancreatic cancer. It provides relief of pain, obstructive jaundice, gastric outlet obstruction, and pancreatic exocrine insufficiency. 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 [69]. Furthermore, the incidence of venous thromboembolism is four to seven folds higher in patients with pancreatic tumor than in other common adenocarcinomas [70]. Options for palliation of jaundice in patients who have obstructive jaundice from locally advanced unresectable pancreatic tumors 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 (Choledochojejunostomy) [71]. It is estimated that 15% to 20% of the patients with pancreatic cancer will develop duodenal obstruction leading to gastric outlet obstruction which is not present at the time of diagnosis [71]. Endoscopically placed expandable metal stents are generally 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 [72]. Approximately 60% of the patients with pancreatic cancer have slowed gastric emptying without evidence of gastroduodenal tumor invasion [73]. Vomiting is often difficult to control but prokinetic agents may likely be helpful [72]. Palliation of pain can be successfully achieved by the use of opioid analgesics alone. Pain control may also be achieved using transdermal patches for patients for whom taking oral medications is difficult. Pain can also be managed with celiac plexus neurolysis and radiation therapy [74]. For reducing steatorrhea and preventing weight loss pancreatic lipase is swallowed during each full meal. In Phase II trials of combination chemotherapies have shown encouraging palliative benefit, objective response rates, and survival outcomes [69]. The phase III trials would likely to confirm these benefits.

Conclusion

Current therapies for human pancreatic cancer are not much successful. The available therapeutic agents often result in profound toxicity and the development of resistance. The use of therapeutic agents targeting multiple signaling molecules and the ongoing clinical trials using combination of vaccines and immuno-modulatory agents proved patient outcomes. However, more deep understanding of the biology of pancreatic malignancy as well as use of more precise drugs combinations predicts the effective therapy of this deadly cancer.

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