Research Article

Pancreatic Cancer and its Treatment: An Insight into its Recent Developments

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ABSTRACT

Pancreatic cancer is known for its unobservable signs and symptoms, rapid growth and resistance to available treatment modalities. Pancreatic cancer is of two types; exocrine pancreatic cancer and NETs. Methods of treatment vary from surgical procedures to radiotherapy to chemotherapy/ other drugs either as monotherapy or a combination of any of the above therapies. However, studies have shown that such cancers are resistant to treatments that are available hence research is now targeting towards newer methods of treatment of pancreatic carcinoma. Various chemotherapeutic drugs individually or in combination are the mainstay in treatment of pancreatic carcinoma that cannot be surgically removed. Current research has now better understood the differences that occur in pancreatic cancer and have used this new set of information to identify new treatment modalities. This review article is to describe all the available treatment modalities available and focus on the newer methods of targeting pancreatic cancerous growth and spread.

Keywords: Pancreatic cancer, advances in pancreatic cancer, pancreatic cancer pathophysiology, pancreatic cancer treatment.

INTRODUCTION

Pancreatic cancer is known for its rapid growth and spread and un-identifiable signs and symptoms, along with its resistance to various treatments that are available in the current field of healthcare. It is said that 97% of patients do not have a lifespan of greater than five years after a confirmed diagnosis. The National Cancer Institute had claimed that there 48,960 new cases of pancreatic carcinoma will be found out in U.S in 2015 and almost the number of deaths caused by pancreatic cancer also will be similar.[1] The pancreas is a flattened organ of the body situated between the liver and the stomach which is located deep inside the abdomen. As it is located deep inside the human body, the pancreatic tumor is rarely palpable and symptoms do not appear until the tumor is large enough. The function of pancreas is parted into the exocrine and endocrine functions. The major portion of pancreas is composed of exocrine cells (acinar cells) which produces enzymes that help to digest food whereas the endocrine cells consist of islets of langerhans which secretes hormones like insulin and glucagon which helps in blood glucose control.[2]

Pancreatic carcinoma are of two types mainly, exocrine tumors which originates in cells of the exocrine pancreas. These cells produce pancreatic juices containing enzymes and the endocrine tumors are the hormone producing cells called endocrine cells.

Pancreatic tumors are also categorized according to where they are in the pancreas. Cancer can grow anywhere in the pancreas, about 65% of tumors start in the head of the pancreas, in body and tail it is 30% and 5% can be from the whole pancreas. The form of cancer is exactly assumed by tissue sample observed by microscope. The most common type of pancreatic cancer is exocrine tumors about 95% which can occur anywhere along the length of the pancreas. The most common form is pancreatic ductal adenocarcinoma (PDAC) and contributes to about 90% of all exocrine cancers. The remaining forms of exocrine cancers are rare.

Various techniques that are used in the diagnosis of pancreatic tumors are used alone and in combination for accurate diagnosis of its presence and type. The main signs and symptoms are Trousseau sign (migratory thrombophlebitis) and venous thrombosis, weight loss, mid-epigastric pain, unrelenting pain, diabetes mellitus, painless obstructive jaundice, pruritus, depression, Courvoisier sign (palpable gallbladder), ascites, palpable abdomen, hepatomegaly and spleenomegaly. In advanced disease there are paraumbilical subcutaneous metastases, palpable metastatic rectal pouch and also palpable metastatic cervical nodes.[3] Pancreatic cancer is tough to be detected in its initial stages and is rarely identified in routine physical examinations since the organ is located deep inside the body and is not easily palpable. Signs and symptoms tend to appear once the tumor has spread to other organs, it is said that pancreatic cancer itself does not exhibit characteristic signs and symptoms.[4]

In resectable pancreatic cancers there is elevation in serum amylase/lipase levels and this is less in unresectable cancers. Obstructive jaundice results in elevated bilirubin, alkaline phosphatase, gamma-glutamyl transpeptidase and only less hike in aspartate aminotransferase and alanine aminotransferase. The

advanced pancreatic cancers and weight loss are evidence of malnutrition.5 Medical history and physical examination may include taking a detailed history, focused examination on the abdomen, and signs and symptoms of jaundice.4

The tumor markers like carbohydrate antigen (CA) 19-9 are present in the biliary tract so it may be high in acute or chronic biliary disease. The normal range is less than 33-37U/ml. In pancreatic patients more than half have CA19-9 levels elevated. This tumor marker is used to evaluate the resectability potential of pancreatic cancer along with imaging studies. The low levels of CA19-9 (<100IU) is indicative of not having an occult metastatic disease and if no biliary obstruction present a high CA19-9 levels would indicate progressive disease. Next tumor marker is carcinoembryonic antigen (CEA) which is a nonspecific and non-sensitive marker and used in gastrointestinal malignancies. The normal level is </=2.5mg/ml. Only less than half of pancreatic cancer patients have this marker elevated.

Genetic testing can also be used especially for those who are at an increased risk due to family history or due to a genetic syndrome.4 Computer tomography (CT) scan is used to see the whole abdomen and pelvis and remains the first diagnostic criteria for suspecting pancreatic cancer. The multi- detector CT angiography is mainly used for pancreatic imaging. But small tumors can still be missed with advanced CT. Transcutaneous ultrasonography (TUS) is comparatively less expensive and is less useful in pancreatic cancer than CT and only 60-70% of pancreatic cancers can be detected using TUS. Because the pancreas is deep in the abdomen TUS is in low frequency which results in low resolution ultrasonogram.

Endoscopic ultrasonography (EUS) uses high frequency ultrasonographic transducer which is used to see the pancreas and unlike sedation is required for this process. EUS is regarded as most sensitive and specific for the pancreatic cancer. The Endoscopic ultrasonography - guided fine needle aspiration is used to confirm pancreatic cancer. EUS and CT scanning are not capable to detect occult nodal involvement. Endoscopic retrograde cholangiopancreatography (ERCP) is used to detect pancreatic, biliary ductal abnormal findings in pancreatic cancer and about 90-95% patients with pancreatic adenocarcinoma show abnormal ERCP. ERCP have a 5-10% risk so is used for therapeutic procedure and also in unusual pancreatic cancers (intraductal pancreatic mucinous neoplasms).

Magnetic resonance imaging (MRI) used for liver lesions characterization which are not applicable by CT. MRI in pancreatic cancer is less well studied as compared to CT. Positron emission tomography (PET) is mainly used for visualization of primary tumor and metastatic disorder. The use of 18F- fluorodeoxyglucose for imaging and they do not provide any additional benefit when used alone but when combined with CT they are more sensitive in detecting pancreatic cancer. Needle aspiration is done to analyze cytology or tissue of pancreatic cancer before a surgery is controversial. EUS guided biopsy is found to be more effective for an accurate cytological diagnosis of pancreatic carcinoma and it involves a relative low risk.

Staging of pancreatic carcinoma is very important after the diagnosis has completed. The pancreatic tumors are grouped into resectable, unresectable and borderline resectable. About 20% of patients presenting with pancreatic tumor are having easily resectable tumors and noncurative resections have no survival benefit. Staging of pancreatic carcinoma are classified by the tumor, node, metastasis (TNM) and this staging system is modified by the American Joint Committee on Cancer (AJCC) in 2002.

Before resection, some institutions perform a staging laparoscopy as to avoid patients with liver or peritoneal metastases to undergo unnecessary surgery that can produce more harm and cure/relief. The staging laparoscopy should be used in patients with CA19-9 level >150 U/ml, low volume ascites, tumors in body of pancreas, borderline resectable tumors, tumor size >3cm and a common bile duct lymphadenopathy.[5]

New innovations in pancreatic cancer diagnosis have evolved and studies have shown that pancreatic carcinoma is not forming suddenly and it forms as a series of stages called pancreatic intraepithelial neoplasia or Pain after many years, which is used to perform tests for analyzing acquired changes in gene for pancreatic carcinoma and identify pre-cancerous conditions. The common DNA changes occur is the KRAS oncogene, which is responsible for the regulation of cell growth but is not recommended for patients who do not have any symptoms.

METHODOLOGY

Relevant studies were analyzed through PUBMED and MEDLINE using MeSH search strategy by typing in the phrases, “pancreatic cancer”, “advances in pancreatic cancer”, “pancreatic cancer pathophysiology”, and "pancreatic cancer treatment and management". All articles that have been published from 2007 onwards were selected from all types of journals; national and international. References from recognized studies, as well as from the previous review, were also scanned to identify any other relevant studies.

Treatment and management of pancreatic carcinoma

Management of pancreatic carcinoma consists of non pharmacological and pharmacological modalities. Treatment options vary from patient to patient depending on the type and stage of tumor as well as other modalities such as availability and cost of medications and procedures. Treatment modalities can generally be classified into: surgery, ablation or embolization therapies, radiation therapy, chemotherapy and other drugs.[4] Till now surgical resection of the pancreas is the most potential curative treatment.[7] It is

stated that only 15-20 % of patients are subjected to pancreatectomy due to the late presentation of the disease. Nevertheless surgery is not possible for all patients especially in developing countries due to the cost of conducting surgeries, i.e. socioeconomic factors.8 Surgery for pancreatic cancer can be curative surgery or palliative surgery. To determine which surgery is the best for the patient, a staging laparoscopy is conducted.[4]

Ablation or embolization therapies for pancreatic cancer

The method is used when the cancer has spread to other organs; usually liver. Usually used in combination with other methods of treatment as means to prevent or relieve cancer symptoms especially pancreatic neuroendocrine tumors (NETs) and/or exocrine pancreas cancers. Ablative treatments used to destroy tumors use extreme temperatures (hot/cold) and include radiofrequency ablation (RFA), microwave thermotherapy, and cryosurgery. Embolization attempts to block the blood supply to cancerous cells by injecting substances in the respective arteries. The three main forms of embolization include arterial embolization, chemoembolization, and radioembolization. Arterial embolization is done by inserting a catheter up until it is in the artery that supplies the tumor. Substances are then inserted into the artery that has been identified so that blood supply to the tumor is blocked. Chemoembolization is a combination of both embolization and chemotherapy. It involves the use of tiny beads that release chemotherapeutic drugs for embolization. Radioembolization is a combination of embolization and radiation therapy. In this procedure radioactive beads are inserted into the targeted artery and once lodged into the artery small amounts of radiation are released over time (days). Since the radiation is travelling a short distance, therapy is limited to the tumor.

Radiation

Radiation therapy targets killing cancer cells with the high energy x-rays. Radiation is used in some exocrine pancreatic cancers. It can also be given after surgery, for borderline resectable tumors, patients who are eligible for surgical procedures, and can also be used to relieve symptoms of cancer.

Resectable cancer

Surgery is preferred in such cases where the cancer has not spread and hasn't reached the large blood vessels. If the patients seem fit for surgery and during the surgery if it is found that the cancer cannot be completely removed then either the surgery is stopped or it is removed in smaller surgical procedures. If surgery has been able to remove the cancer, chemotherapy as monotherapy or in combination with radiation therapy may be given to ensure complete or close to complete eradication of the cancerous cells.[4]

Borderline resectable cancer

If the tumor has not developed too deeply into the blood vessels surgery may be conducted in attempts to remove the cancer as much as possible. These are often treated with neoadjuvant chemotherapy in attempts to reduce the size of the tumor and to allow the removal of the cancer to be made easier.

Adjuvant therapy for resected exocrine pancreatic carcinoma

Post-operative adjuvant therapy is recommended to be given to all patients who had undergone resection of an exocrine pancreatic carcinoma. There are some reports stating that the option of adjuvant therapy should only be given to those based on postoperative CA 19-9 levels, however other reports state that these values should not be used as a sole basis on whether patients should be given adjuvant therapy.[9] It is recommended that adjuvant therapy should be started immediately after surgery despite high morbidity rates after surgery. As of yet there is no evidence of randomized trials concerning the impact of delayed initiation of adjuvant therapy on outcomes or the effect of a longer duration of therapy.[10] Ideally the therapy should start within 4-6 weeks and continued for a total of 6 months.[11] Pancreatic carcinoma is known for its high rate of systemic and local recurrence and one of the goals in advanced treatment and management is to enhance patient outcomes through the use of both chemotherapy and radiation therapy.[12] The reduction on systemic recurrence has been profoundly decreased with the adjuvant chemotherapy of fluoropyrimidines and gemcitabine. Adjuvant radiation therapy has also shown decreased in local recurrence of the carcinoma. As per American clinicians the utilization of FU included concurrent chemoradiotherapy in add on to four months of adjuvant gemcitabine therapy is the most followed approach.[13]

According to guidelines for the national comprehensive cancer network (NCCN) a history and physical assessment for symptoms to get assessed every three to six months for two years, then annually with low level of evidence. NCCN also suggest the usage of CA 19-9 determinations and follow up CT scans at three to six month intervals for two years after a surgical resection, then annually. As for the other hand consensus based guidelines from the European society of medical oncology (ESMO) recommend that the post treatment surveillance strategy be individualized to lessen emotional stress and economic burden. In addition to repeat CT scans of abdomen and pelvis every 6 months, they suggest monitoring CA 19-9 levels every three months for two years if CA 19-9 levels were elevated preoperatively.[14] Nevertheless there is still no clarity regarding the early initiation of treatment in asymptomatic individuals and association with a survival benefit therefore questioning the so called surveillance technique.15 Despite the confusion majority of the clinicians still favor to follow NCCN guidelines.[16]

Initial chemotherapy and RT for patients with non-metastatic locally advanced unresectable, borderline resectable and potentially resectable exocrine pancreatic carcinoma.

The standard approach in the treatment of locally advanced unresectable and borderline resectable tumors is surgery which is followed by adjuvant therapy; however, the management is now in the process of transformation.[17] The use of neoadjuvant chemoradiotherapy in pancreatic carcinoma is associated with high rates of tumor fibrosis in pathologic specimens and higher rates of an R0 resection (no gross or microscopic cancer remains in the primary tumor bed), which is likely to contribute to the lower rates of local recurrence shown in patients undergoing pancreatectomy after neoadjuvant chemoradiotherapy is completed.[18] Nevertheless, points to be considered before deciding which treatment is ideal on an individual patient basis include a tissue diagnosis and for those patients who present with obstructive jaundice. The delivery of neoadjuvant therapy can cause durable biliary decompression for six months.[19]

Locally advanced unresectable disease

The current recommendation for those patients with locally advanced unresectable disease, an initial period of chemotherapy should be started, followed by an intermediate radiation therapy of chemotherapy[20] for patients who have an excellent performance status (which is the total bilirubin level that is below 1.5 times the upper limit of normal and who are able to tolerate it). It is suggested that a combination therapy such as FOLFIRINOX should be started[21] and for those who do not progress following initial chemotherapy a combined treatment of external bean RT (EBRT) plus concomitant low dose infusion FU should be a possibility.[22] This treatment is also consistent with published guidelines from the NCCN 8 and ESMO 9. Stereotactic body radiotherapy (SBRT) is also another treatment option. However trials comparing the efficacy of SBRT and standard fractionation external beam RT have yet to be conducted.[23] RT, used as monotherapy, is considered for palliative pain purposes for those who are not considered suitable for combined chemoradiotherapy due to medical comorbidities or those whose pain is not adequately controlled even with the use of narcotic analgesics.[24] Another recommended option in those situations is plexus nerve block.[25] Gemcitabine alone as monotherapy is now commonly practiced. However, combination therapy is also another option that is being considered in the current clinical setting. A major drawback is the lack of trials available comparing the combination therapy to gemcitabine monotherapy alone in individuals with locally advanced disease.[26] FOLFIRINOX is being commonly used, however, due to its toxicity profile. Patients should be carefully chosen for this treatment modality. There are many gemcitabine combinations available. However, as of yet, there are no published data for gemcitabine plus nab-paclitaxel. A phase II trial evaluating the neoadjuvant gemcitabine plus oxaliplatin in patients with initially unresectable (n=18) or borderline resectable (n=15) non metastatic pancreatic carcinoma showed that 40% had sufficient tumor regression to undergo operative resection, which was complete in 69%.[27]

A combination of paclitaxel and EBRT has also been studied.[28] Results are, however, limited but promising. A report has shown that 11 out of 42 patients having locally advanced disease who were treated with paclitaxel 50mg/m^2 per week and concurrent EBRT (50.4 Gy) obtained a partial response. 14 patients with initially unresectable disease then underwent surgical re exploration and four could be completely resected. It is suggested that further studies regarding the use of paclitaxel as a radiation sensitizer off protocol[29] require further evaluation and assessment.[30]

Metastatic cancer

Such cancers have spread to many organs and surgery is not a viable option. In such cases, chemotherapy is the main method of treatment. Gemcitabine is used often as well as FOLFIRINOX.[4]

Targeted therapies

The aim of targeted therapies is to concentrate the mode of action of agent to specific proteins. It was thought to be more effective with fewer side effects.

The researchers have studied more about what makes pancreatic cancer cells different from normal cells. They have developed newer molecules that should be able feat these differences by attacking only specific targets. These targeted therapies may provide better options in pancreatic cancer treatment. They may prove to be useful along with, or instead of, current treatments. In general, compared to traditional chemo drugs newer ones are having fewer side effects than.[31] (a) Sunitinib acts on the development of new blood vessels, has shown to slow the rate of tumor growth and increases patient's length of life. This drug is also advantageous in having to be taken in as a once daily oral dosing. (b) Everolimus acts by blocking a cell protein called mTOR which is needed for cellular growth and division. This drug is also taken as a once daily dosing in oral dosage form; it is known to slow the growth of the tumor. However, its effect on patient's life span is not yet fully studied.[4]

Looking for new targets to attack on cancers is an active area of research. Anti-angiogenesis factors are meant to hinder the growth of these vessels and allow the tumor to be malnourished. Researchers are also searching for agents that target the tumor stroma to inhibit the protection of tumor cells from chemotherapeutic drugs by breaking the barrier down.

A current active research in all forms of anti-cancer agent monoclonal antibodies is also having its share in the treatment of pancreatic carcinoma. However, they are currently being applied in clinical trials only.

The proposal of vaccines for hiking the immune system response to pancreatic tumor cells is another 'hot topic'. Again they have only been tested in clinical trials. However, it is believed to have fewer side effects than the presently available chemotherapeutic agents.[31]

Despite the many options of adjuvant therapy treatment and management modalities available for pancreatic cancer there is still an outstanding unresolved issue of "post treatment surveillance". It is suggested that guidelines in following up patients after completion of adjuvant therapy need to be developed and implemented in daily practice. It is stated that 'majority of recurrences after potentially curative treatment of pancreatic exocrine cancer occur within two years.[16]

Molecularly targeted therapy

Considerable research has been conducted with regards to the Ras protein. From the research available, mutations of this gene present in 90% of pancreatic carcinomas. Current research is aimed at targeting these genes. The main aim in research is to block the addition of these proteins to the cellular membrane of pancreatic cells.

Hormone therapy

Studies have found that tissues containing estrogen and somatostatin are present in normal and malignant pancreatic tissues. Hence, agents such as tamoxifen and octreotide have been implemented in clinical trials however have so far not shown any advantageous results. The observation that normal and malignant pancreatic tissues contain estrogen and somatostatin receptors provided the rationale for hormone manipulation in advanced disease.[4]

Palliative care

Not only is the treatment and management necessary for pancreatic carcinoma, its palliative care is an area that clinical pharmacist's should not overlook. The aims of palliative therapy is to control the symptoms of unresectable or recurrent pancreatic carcinoma, to provide relief of pain, obstructive jaundice, gastric outlet obstruction, and pancreatic exocrine insufficiency.32 As well as other conditions that are commonly associated with pancreatic cancer such as depression should be areas where clinical pharmacists expertise is vital to ensure the rational, safe and effective use of drugs.[33]

Although no regimen has been proved substantially more effective than others, 6 months of adjuvant therapy with 5-FU based or gemcitabine based chemotherapy is considered as a standard therapy.[34]

DISCUSSION

A review in current clinical pharmacology journal showed that the usual treatment with 5 fluorouracil and gemcitabine have showed success in pancreatic cancer in the past but new treatment strategies have to be developed due to lack of choice in pancreatic cancer treatment. Now there is ongoing investigation of some novel drugs like doxycycline and doxorubicin and some dietary components like curcumin and genistein for the use in pancreatic cancer. Each drug has different activities as a monotherapy agent and in combination with gemcitabine.

A review in Current Opinion in Gastroenterology shows the importance of new developments in the imaging techniques in pancreatic disorders and the ability to detect malignancies, inflammation, to grade pancreatitis and to stage the pancreatic cancer precisely. This study portrays that the computed tomography severity index for grading acute pancreatitis and magnetic resonance imaging are comparable. Contrast enhanced ultrasonography helps in analyzing the inflammation and fibrosis in autoimmune pancreatitis and in detecting the response to steroid therapy. The staging of pancreatic carcinoma is done best with contrast enhanced ultrasonography and also positron emission tomography or computed tomography improves detection of neuroendocrine tumors.

Study in The Oncologist Journal showing the use of gemcitabine in combination with targeting human epidermal growth factor receptor (HER-1/EGFR) showed significant survival rate improvement over gemcitabine alone. The U.S. Food and Drug Administration approved erlotinib (HER-1/EGFR tyrosine kinase inhibitor) combined with gemcitabine as the first-line treatment of advanced pancreatic carcinoma. Cetuximab (anti HER-1/EGFR monoclonal antibody [mAb] with gemcitabine showed no increase in survival rate as compared to gemcitabine alone but targeting vascular endothelial growth factor(VEGF) with bevacizumab (recombinant, humanized IgG1mAB) in combination with gemcitabine was successful initially but failed in subsequent study.

A review article in Current opinion in Gastroenterology revealed that in severe acute pancreatitis, pancreatitis is managed with early intensive therapy and late surgical debridement and for chronic pancreatitis. Treatment by preserving pancreatic head resection with an inflammatory mass of the head is found to be superior to pylorus-preserving Whipple resection. In cystic neoplasia, local organ preserving resection techniques showed less morbidity and mortality compared to the Whipple type resection. But resections in pancreatic carcinoma patients are found to be ineffective to cure and after an R0 (resection for cure or complete remission) resection, there is a significant benefit with adjuvant chemotherapy.

In a study in Current Opinion in Genetics & Development showing the development of cancer stem cells in solid cancers, the theory involved in the cancer stem cells is that a cancer cell within a tumor has the capacity to self renew and differentiate. This is applied to leukemia where only cells with specific surface antigens are causing leukemia in mice. Now solid tumors were using the similar technique in mice and human tumors (e.g. tumors

of pancreas, breast, brain and colon) dependent on cancer stem cells.

A new drug has been approved by U.S FDA, on October 22 2015, via- the Irinotecan liposome injection (Onivyde®) which is used in combination with fluorouracil and leucovorin. This drug is recommended for those who have previously treated with gemcitabine based chemotherapy. A three arm, randomized, open label study of 417 patients of metastatic pancreatic adenocarcinoma whose cancer increased even after receiving gemcitabine or a gemcitabine based therapy were included in the study. It was found that those who were treated with Onivyde alone or in combination with fluorouracil/leucovorin lived longer than those receiving the same treatment without onivyde. It was also observed that there was a delay in the time for tumor growth with the combination than those who had received fluorouracil/leucovorin. This drug, that is marketed by Merrimack Pharmaceuticals Inc. of Cambridge, Massachusetts and includes a boxed warning of severe neutropenia and diarrhea and is not approved to be used as a single agent in the treatment of metastatic pancreatic carcinoma.[1]

CONCLUSION

Our review focused on the available treatment approaches and the recent updates of pancreatic cancer therapy. All patients with locally advanced or metastatic disease will have an extremely poor prognosis. Even in the absence of effective screening methods, considerable efforts have been made during the past decade to assess effective treatment modalities. The truth is that most trials have not shown a survival benefit for most of the existing treatments. Preclinical and clinical studies of pancreatic cancer development revealed that while current regimens are ineffective, the new developments provided some optimism that new drugs inhibiting specific targets will enhance patient outcome and overcome the resistance of pancreatic carcinoma to most standard treatments.

Recent advancement in pancreatic cancer treatment with Folfirinox® and Onivyde® improved treatment efficacy in the field of palliative chemotherapy. Strategies have to be designed to raise the research and clinical practice in this area in order to ensure the best treatment for pancreatic carcinoma patients. Hence our insight in the current standards of patients care with locally advanced and metastatic pancreatic cancer can provide health care and research team more concerns into the matter.

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