Pancreatic Cancer:
Review of Etiology, Clinical Features,
Diagnostic Procedures, Treatment and Mesothelin Role

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ABSTRACT

Pancreatic cancer is one with high mortality cancer in the world. Ninety percent of pancreatic cancer is pancreatic adenocarcinoma. Various factors is associated with an increased risk of pancreatic cancer including age, sex, race, genetic, history of chronic pancreatitis, diabetes mellitus, gallstone, obesity, Helicobacter pylori infection, smoking, diet, and polution exposure. A lot of cases were diagnosed in late stadium due to non-specific early clinical symptoms, and also, until now, there is no examination tool that may screen pancreatic cancer in the earliest stage. Total surgery resection is the therapy of choice in the early stadium of pancreatic cancer, and other therapy modalities are chemotherapy, radiotherapy. Combination of these modalities is frequently used in order to increase the effectiveness of therapy. Mesothelin, a surface glycoprotein on normal mesothelial cells, is overexpressed in pancreatic cancer; therefore, although it is not a cancer specific antigen, it can be used in diagnostic and treatment of pancreatic cancer. Several studies about mesothelin application in pancreatic cancer have been performed; however, more studies are needed to improve the application of mesothelin on pancreatic cancer.

Keywords: pancreatic cancer, risk factor, therapy, mesothelin

ABSTRAK

Kanker pankreas merupakan salah satu kanker dengan tingkat mortalitas yang tinggi di dunia. Sembilan puluh persen kanker pankreas merupakan adenokarsinoma pankreas. Berbagai faktor berhubungan dengan peningkatan risiko kanker pankreas antara lain usia, jenis kelamin, ras, genetik, riwayat penyakit pankreatitis kronis, diabetes mellitus, batu empedu, obesitas, infeksi Helicobacter pylori, merokok, pola makan, dan paparan polusi. Gejala klinis yang tidak khas menyebabkan banyak kasus terdiagnosis saat stadium lanjut. Selain itu belum ada pemeriksaan penunjang yang dapat menyaring kanker pankreas secara dini hingga saat ini. Pilihan terapi yang tersedia adalah bedah, kemoterapi, radioterapi dengan bedah reseksi total merupakan terapi kuratif utama. Kombinasi modalitas terapi tersebut sering digunakan untuk meningkatkan efektivitas terapi. Mesotelin, glikoprotein permukaan sel mesotelial, banyak diekspresikan pada kanker pankreas, meskipun bukan merupakan antigen spesifik kanker tetapi dapat digunakan dalam diagnostik dan tatalaksana kanker pankreas. Beberapa penelitian mengenai aplikasi mesotelin pada kanker pankreas telah dilakukan, tetapi penelitian lebih lanjut masih diperlukan dalam mengembangkan aplikasi mesotelin pada kanker pankreas.

Kata kunci: kanker pankreas, faktor risiko, terapi, mesotelin

INTRODUCTION

Pancreatic cancer is one of the deadly cancers in the world. The statistics in the United States (US) in 2007 showed that pancreatic cancer ranks fourth as a cause of cancer death in male and female. Five year survival rate of pancreatic cancer in the US, although showing an increase, but the lowest when compared with survival in other cancers, there are 3% (1975-1977), 3% (1984-1986), 6% (1999-2005) on white race and 2% (1975-1977), 5% (1984-1986), 5% (1999-2005) at the African American race. In the year 2010 is estimated that there are 21,370 new cases of pancreatic cancer in male and 21,770 new cases in female, while the mortality rate is estimated at 18,770 in male and 18,030 in female.[1] In Japan, pancreatic cancer is the fifth largest cause of death for cancer, of which 70% are found more common in male than female.[2] There is no much data on pancreatic cancer in Indonesia. A study in Semarang reported 53 cases of pancreatic cancer between the years 1997-2004.[3] According to statistics in Indonesia in 2004-2007, pancreatic cancer is not included in the top 10 cancers.[4]

The high mortality rate of pancreatic cancer may due to no typical early symptoms; moreover, the cancer is rapidly spread to the lymphatic system and distant organs. Therefore, 80% of patients have already had locally advanced stage or metastases when the diagnosis is established. Consequently, curative therapy is more difficult in this condition. In addition, 80 % of patients experience recurrence after curative surgery in the first 2 years.[5,6,7]

ETIOLOGY AND PATHOGENESIS

Histologically, pancreatic cancer can be derived from exocrine or endocrine pancreatic tissue. The majority (90%) of pancreatic cancer originates from the exocrine tissue of pancreatic ductal adenocarcinoma.[3,8] Approximately, 70% of pancreatic cancers occur in the head of the pancreas, 20% in the body, and 10% in the tail of the pancreas.[3,9] The term pancreatic cancer used in this article is referred to exocrine pancreatic cancer tissue.

The main etiology of pancreatic cancer is still being studied until now, but several factors may increase the risk of pancreatic cancer, which is an interaction between exogenous and endogenous factors. Exogenous risk factors are smoking, diet, exposure to pollution; while the endogenous risk factors are age, sex, race, genetics, history of chronic pancreatitis disease, diabetes mellitus, gallstones, obesity, gastric infection by *Helicobacter pylori* (*H. pylori*).[3,9,10]

Smoking is the greatest risk factor for pancreatic cancer. The result of meta-analysis of 82 studies published between 1950 and 2007 showed that active smokers had an increased risk of pancreatic cancer about 1.74 times (95% CI = 1.61-1.87), while it was about 1.2 times (95% CI = 1.11-1.29) in former smokers. This risk lasted at least 10 years after one stopped smoking.[11] A prospective cohort study in Japan showed a correlation between smoking and increase of mortality due to pancreatic cancer in male and female with relative risk of 1.8 (95% CI = 1.3-2.4).[12]

Food consumption plays a role as a risk factor for pancreatic cancer. The study by Morales et al showed that people consuming milk or milk products every day had a tendency of suffering exocrine pancreatic cancer with 5 times greater of K-Ras mutation [odds ratio (OR) = 5.10; p = 0.04]. In addition, K-ras mutation also occured in people who had low intake of polyunsaturated fatty acids (PUFAs), omega-3 and vitamin E.[2,13] High meat consumption is associated with increased risk of pancreatic cancer by 26% (95% CI = 1.02-1.56). Risk of pancreatic cancer is mainly on the consumption of red meat and processed meat at high temperatures.[14]

Exposure to certain substances in the environment is associated with the risk of pancreatic cancer. Exposure to benzene is significantly associated with mutations in K-ras gene (OR = 7.07; p < 0.05). Moreover, hydrocarbon exposures are strongly associated with mutation codon 12 from glycine into valine or aspartic acid on K-ras gene.[15]

Factors of age, sex, and race are reflected in epidemiological data of pancreatic cancer. Pancreatic cancer is rarely found at age < 50 years. Data in the United States in 2007 showed that pancreatic cancer is the largest cause of death in male and female patients aged > 40 years, with the highest rate in the age group of 60-79 years.[1] The number of deaths due to pancreatic cancer in the US are more in male than female, while the incidence of pancreatic cancer is a little more common in female than male. In Japan, however, the data of pancreatic cancer incidence rate in male is higher than female, which is 17.7 : 14.0.[1,16] In this case, the role of hormonal factors in pancreatic cancer is still under study.[17] Race-related factors in the pancreatic cancer are seen in the molecular differences between races. K-ras mutation into valine is more common in Afro-Americans (58%) than Caucasians (22%) with p = 0.015.[2,18]

Genetic predisposing factors play a role in 10% of patients with pancreatic cancer. The most common disorder is the BRCA2 gene mutation. Abnormalities of chromosomes, such as the hereditary nonpolyposis colon cancer (HNPCC), familial atypical malignant melanoma syndrome (FAMMM), hereditary pancreatitis, are associated with an increased risk of

pancreatic cancer.[2,3] History of chronic pancreatitis disease is associated with pancreatic cancer. In 1993, Lowenfels et al conducted a multicenter study using historical cohort design of 2,015 patients with chronic pancreatitis showing pancreatic cancer incidence ratio of 26.3 (95% CI = 19.9-34.2), and the risk increased together with the duration of pancreatitis, i.e. 1.8% after 10 years and 4% after 20 years being diagnosed.[19]

There is a correlation between diabetes mellitus and the occurrence of pancreatic cancer. Lin et al performed a large-scale prospective cohort study and found that the risk of pancreatic cancer increased in male having a history of diabetes mellitus with risk ratio (RR) = 2.12; 95% CI = 1.19-3.77. Moreover, the study also suggested that a history of gallstones or cholecystitis was associated with increased risk of pancreatic cancer deaths in female with RR = 2.51; 95% CI = 1.41-4.46.[20] A case-control study conducted by Li et al showed that overweight at age of 14-39 years (body mass index (BMI) = 25 - 29.9 kg/m^2) and obesity at age 20-49 years (BMI $\geq$ 30 kg/m^2) increased the risk of pancreatic cancer respectively 1.67 times and 2.58 times, regardless whether the subject suffered from diabetes mellitus. There was also a stronger correlation in male than female subjects and in smokers than non smokers.[21] The presence of *H. pylori* gastric infection with CAG+ strains causing peptic ulcers and gastric cancer may also be associated with the risk of pancreatic adenocarcinoma. Stolzenberg-Solomon et al in the case-control study in Finland found that subjects with serological *H. pylori* positive had an increased risk of pancreatic cancer (OR 2.87; 95% CI = 1.05-3.34).[22]

CLINICAL MANIFESTATIONS

Early symptoms of pancreatic cancer are not typical; therefore, most cases have already been at advanced stage at the time the cancer is diagnosed. Initial complaint is not typical such as nausea, vomiting, bloating, steatorrhea. The three main complaints are abdominal pain that may spread to back, weight loss > 75%, jaundice due to biliary tract obstruction, with 80-90% cases are carcinoma of pancreatic head. In addition, Courvoisier sign may also be found in obstruction case due to head cancer of the pancreas, glucose intolerance, vein thrombosis, migratory thrombophlebitis or Trousseau sign, periumbilical nodules or Sister Mary Joseph's nodule, hepatosplenomegaly, gastrointestinal bleeding and ascites.[3,9]

LABORATORY AND IMAGING TESTS

Nowadays, there are some laboratory and imaging tests supporting the diagnosis of pancreatic cancer, such as tumor markers of carcinoembryonic antigen (CEA), carbohydrate antigen (CA 19-9), ultrasonography, computed tomography (CT), endoscopic retrograde cholangio-pancreaticography (ERCP), magnetic resonance image (MRI), and positron emission tomography (PET) scans.

CEA is a glycoprotein with high-molecular weight that is normally found in fetal tissue. In pancreatic cancer, there is an increase of CEA, but it may also be found in other organ cancers. Therefore, CEA is not a specific marker for pancreatic cancer.[3] CA 19-9 is one marker for pancreatic carcinoma that is widely used today. CA 19-9 examination is an examination of monoclonal antibodies against antigens that are normally found in circulating mucin in cancer. Elevated CA 19-9 level may also occur in other gastrointestinal adenocarcinoma such as cirrhosis as well as inflammation of the bile duct and liver.[3,9] The normal range limit of CA 19-9 depends on the intended use. To differentiate benign or malignant tumor, The European Group on Tumor Markers (EGTM) suggests the normal range limit of 37 kU/L.[23] However, The American Society of Clinical Oncology (ASCO) in 2006 did not recommend CA 19-9 as a screening test for pancreatic cancer since its specificity and sensitivity are not sufficient for screening, especially in early stages.[24] To monitor therapeutical response and recurrence after surgical treatment, chemotherapy or radiation, ASCO recommends imaging test and biopsy in addition to CA 19-9.[23,24]

Currently, there are several options of imaging modalities for pancreatic cancer. Bipat et al in a meta-analysis of data in 1990-2003 on imaging modalities for pancreatic cancer suggested that for diagnosis, the sensitivity of helical CT, conventional CT, MRI, ultrasound were 91%, 86%, 84% and 76%, respectively; while the specificity were 85%, 79%, 82%, 75%, respectively. For the determination of resectability, the sensitivity of helical CT, conventional CT, MRI, ultrasound were 81%, 82%, 82%, 83%, respectively and the specificity were 82%, 76%, 78%, 63%.[25] Transcutaneous abdominal ultrasound is useful in for initial screening, especially in patients who come with obstructive jaundice. Endoscopic ultrasonography is useful to overcome the air resistance on the gastrointestinal tract, which occurs in transcutaneous ultrasound and at the same time, it may collect the tissue specimens.[3,26] CT scan is one of the initial imaging modalities for pancreatic cancer that can produce detailed images, especially as technology has been advanced to triple-phase contrast-enhanced CT.[26,27] ERCP is very sensitive to detect abnormalities of biliary duct as well as useful channel for installing the bile drainage stent.[3,26] MRI

has advantages in imaging of pancreatic duct and can differentiate pancreatic cancer with inflammation and cystic lesions.[3,9,26,28]

STAGING AND MANAGEMENT

Management of pancreatic cancer currently has 3 modalities of therapy, i.e. surgery, chemotherapy and radiotherapy. The options of currative surgical resection for pancreatic cancer include pancreaticoduodenectomy (Whipple procedure), distal pancreatectomy, and total pancreatectomy. Total pancreatectomy is the most effective therapy, but can only be applied to about 10-20% of cases only, which have no evidence of metastasis found on chest X-ray examination and abdominal-pelvic CT scan. Metastases have occurred in the majority of cases of pancreatic cancer when the diagnosis is established, i.e. 40% have been at locally advanced stage, either resectable or not (there is involvement of superior mesenteric artery, superior mesenteric vein, celiac axis, inferior vena cava and aorta); 40% had experienced visceral metastases. However, the 5-year-survival rate after total resection is only 10%. Adjuvant therapy can be given before or after surgery, which aims to shrink the tumor size so that ease the process of surgery and the treatment of micro metastasis. Optional available modalities may include chemoradiotherapy, which is usually applied in the case of advanced local stage, and chemotherapy, as well as the cases with metastasis.[9,28]

Chemotherapy in cases of widespread metastases has provided less satisfactory results. Two major chemotherapeutic agents that have been frequently used are 5-fluorouracil (5-FU) and gemcitabine. 5-FU is a pyrimidine analogue which can inhibit the synthesis of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Gemcitabine is an antimetabolite analogue deoxycytidine. Currently, gemcitabine is the standard chemotherapy of choice for pancreatic cancer. It is supported by a phase III clinical study comparing 5-FU with gemcitabine. The study demonstrated clinical response improvement (degree of pain, body weight, Karnofsky performance) 4.8% in 5-FU and 23.8% in gemcitabine (p = 0.0022); the survival rates were 4.41 months and 5.65 months in 5-FU and gemcitabine, respectively.[29] The combined use of chemotherapeutic agents has been extensively studied nowadays in order to improve the therapeutical response. Combination of four chemotherapeutic agents, i.e. cisplatin, epirubicin, gemcitabin, and 5-FU, showed median survival of 10 months in a phase II study of patients with pancreatic adenocarcinoma.[30]

The use of combination chemotherapy agents will certainly increase toxicity, especially hematologic and gastrointestinal systems.[31] Combined chemoradiotherapy can be applied, particularly for cases without metastases. The given chemotherapy agent will increase tumor sensitivity to radiotherapy. However, whether chemoradiotherapy may improve survival of patients with pancreatic cancer remains to be investigated further, because few studies currently have provided different results.[3,32] In addition, palliative symptomatic therapy is often administered, considering that the majority of patients have already been at advanced stage when the diagnosis is established, with the most common complaints are pain and jaundice.[32]

MESOTHELIN AND ITS APPLICATION ON PANCREATIC CANCER

Mesothelin is a glycoprotein which is expressed on normal mesothelial cells lining the pleura, pericardium, and peritoneum. Mesothelin gene encodes a 71-kDa precursor which is then processed into a 40-kDa mesothelin protein and 31-kDa megakaryocyte potentiating factor. Mesothelin is redundantly expressed by some tumors such as pancreas, lung, and ovary; therefore, although it is not a cancer specific antigen, its abnormal expression may be applied in pancreatic cancer.[33,34] A study by Argani et al using serial analysis of gene expression (SAGE) found mesothelin mRNA expression (confirmed by in situ hybridization methods, RT-PCR) and mesothelin protein (confirmed by immunohistochemical methods) in pancreatic cancer. Both of the mesothelin mRNA expression and mesothelin protein were absent in normal pancreas.[35] Li et al also found that mRNA expression increased 17.5 times in pancreatic cancer

Table 1. Staging of exocrine pancreatic carcinoma[3,28]

	M0		M1
	N0	N1*	
T in situ	Stage 0		
T1 (≤ 2 cm), limited to the pancreas	Stage I		
T2 (> 2 cm), limited to the pancreas			
T3 (extends beyond the pancreas, but without involvement of the superior mesenteric artery or celiac axis)	Stage IIA	Stage IIB	
T4 (extends to the superior mesenteric artery, axis celiac, stomach, spleen, colon)	Stage III		Stage IV

*N1 there has been metastases to regional lymph nodes

tissue compared to the adjacent healthy pancreas tissue.[36] Therefore, mesothelin has a potency to be used as a marker in supporting the diagnosis of pancreatic adenocarcinoma.

Excessive expression of the mesothelin in pancreatic cancer can be used as a target-specific antibody therapy since mesothelin can stimulate the formation of monoclonal antibody. One study that is being developed is antimesothelin immunotoxin SS1P against solid cancers expressing mesothelin, such as pancreas. Hassan et al and Kreitman et al had conducted the phase I study on antimesothelin immunotoxin evaluating the dose and route of administration, either by bolus injection or by continuous intravenous infusion.[37,38] However, there has been only little number of pancreatic cancer patients examined in both studies; respectively 2 and 1 subjects since both studies also evaluated other cancers that also express mesothelin (i.e. mesotheliomas and ovarian). Therefore, further studies are necessary.[37,38] Combination of SS1P therapy with other therapeutic modalities is also possible. The increase of mesothelin expression is found on cell surfaces after being irradiated, and it will increase the sensitivity of cancer cells against SS1P. Such mechanism may explains the benefit of combining SS1P therapy with radiotherapy.[39]

Another potency of mesothelin that can be developed is a therapeutic vaccine for cancer. Vaccination with virus like particle (VLP) can increase the concentration of specific antibodies and CD8+ responses. These, may inhibit tumor progression in C57BL/6J mice and increase the specific antibody against mesothelin.[36]

CONCLUSION

Pancreatic cancer is one of the deadly cancers in the world. It is often diagnosed lately at advanced stage due to no typical early symptoms of the cancer. Moreover, no screening test having a good sensitivity to detect the cancer at early stage is available until now.

The most effective curative treatment is total resection; however, the survival rate after total resection is still quite low and only few patients could have total resection. Combination therapies with other therapeutic modalities have not provided satisfactory results. Further studies to find a more sensitive and specific diagnostic tool as well as the more effective treatment modalities for pancreatic cancer are necessary. Mesothelin, a glycoprotein which is widely expressed in pancreatic cancer, has a good potency to be used in diagnosis and treatment of pancreatic cancer.

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