Palliative Management of Advanced Pancreatic Cancer: The Role of Gastroentero-hepatologist

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ABSTRAK

Kanker pankreas umumnya didiagnosa pada stadium lanjut karena sering kali tidak menunjukkan gejala spesifik pada awal presentasi, serta dikaitkan dengan angka kesintasan 5 tahun yang rendah. Hanya sekitar 10-20% pasien yang ditemukan pada tahap dapat dilakukan reseksi atau tahap masih terlokalisir. Beberapa komplikasi dapat muncul akibat kanker pankreas tahap lanjut seperti ikterik obstruktif, obstruksi jalan keluar lambung, cachexia, pruritus akibat kolestasis, dan nyeri kanker. Manajemen paliatif perlu dioptimalkan untuk meningkatkan kualitas hidup pasien. Seorang konsultan gastroenterohepatologi perlu berkoordinasi dengan sejawat spesialisasi lain untuk memberikan perawatan paliatif secara komprehensif bagi pasien kanker pankreas stadium lanjut.

Kata kunci: *kanker pankreas, metastasis, perawatan paliatif, ikterus obstruktif.*

ABSTRACT

Pancreatic cancer commonly diagnosed at late stage due to subtle clinical manifestation and associated with low 5-year survival rate. Only 10-20% of patients were found in resectable or localized stage. Several complications may arise due to advanced pancreatic cancer such as obstructive jaundice, gastric outlet obstruction, pancreatic cancer cachexia, pruritus of cholestasis, and cancer pain. Palliative management should be optimized in order to improve patient's quality of life. A gastroentero-hepatologist should collaborate with other specialties to give comprehensive palliative care for advanced pancreatic cancer patients.

Keywords: *pancreatic cancer, metastases, palliative, obstructive jaundice.*

INTRODUCTION

Pancreatic cancer patients usually have bad prognosis. Due to the subtle presentation at early stage, only 10-20% of patients were found in resectable or localized stage.[1] Even though, in recent decades there are trends in improvement for pancreatic cancer 5-year survival rate, pancreatic cancer remains one of the cancer with the lowest survival rate. Data showed that overall 5-year survival rate of all stages pancreatic cancer is only 5% and as low as 2% in some countries.[1,2]

According to World Health Organization (WHO) GLOBOCAN 2018, pancreatic cancer

ranked twelfth (458,918 cases) among the highest cancer incidence in 2018 and the number fifth most common among all gastrointestinal malignancy cases. WHO GLOBOCAN 2018 also stated that pancreatic cancer ranked seventh (432,242 cases) among all cancer death cases. More than 40% of all pancreatic cancer incidence and death cases derived from Asian countries. Also from WHO GLOBOCAN 2018, pancreatic cancer ranked seventeenth among the highest cancer incidence with 4,940 cases and ranked twelfth among all cancer death cases with 4,812 cases.[3-5]

Considering the lethal nature of pancreatic cancer, high number of incidence and also the fact that most of pancreatic cancer patients were found in unresectable stage, therefore the palliative management for patients with pancreatic cancer should be optimized whenever indicated.[6] The principles of palliative management are to support and treat the physical, mental, and psychosocial health of the patient with advanced disease. Therefore the goal of palliative care should be decreasing stressful disease related symptoms, enhancing quality of life, and improving patients knowledge regarding their disease and acceptance toward their advanced illness.[7] This review was made to highlight the role of gastroentero-hepatologist in management of advanced pancreatic cancer, focused on interventional management for complications related with pancreatic cancer obstruction, and management for nutrition and symptoms related with pancreatic cancer disease.

OBSTRUCTIVE JAUNDICE

One of the most prominent clinical manifestations of pancreatic cancer is jaundice. Jaundice is caused by the obstruction of biliary duct due to the mass effect therefore commonly termed as malignant bile duct obstruction.[8] Up to 70 percent of pancreatic cancer patients presenting with obstruction. Malignant biliary obstruction jaundice caused by biliary duct obstruction may associated with several problems and complications such as pruritus, liver injury, impairing cellular immunity, accelerating tumor growth and metastasis progression, coagulopathy due to impaired vitamin K absorption caused by lack of secreted bilirubin, cholangitis, and bacterial translocation.[9,10] Therefore, biliary decompression and relief for the obstruction are needed to prevent the possible complications related with obstructive jaundice.

Endoscopic Biliary Stenting

Endoscopic retrograde cholangio-pancreatography (ERCP) may become primary option for gastroenterologist to implant stent in malignant related obstructed biliary duct.[11] Stent placement may facilitate biliary drainage which may become feasible option as bridging therapy for patients with resectable pancreatic cancer before surgery schedule. Some studies showed preoperative biliary drainage increased complication compared with patients who had not preoperative drainage.[12] However, consideration regarding the benefit of preoperative drainage should be carefully made such as in patient with condition of intractable pruritus, acute cholangitis, and need for neoadjuvant therapy. Therefore in guideline issued by European Society of Gastrointestinal Endoscopy (ESGE) recommended against routine preoperative biliary drainage except in selected cases as aforementioned before.[12] Protocol for reducing post ERCP related complications should be carefully employed as adequate hydration, careful maneuver, and rectal indometachin administration.[12,13] Comparison between biliary stenting and surgical bypass always become debatable field. Several meta-analysis showed that endoscopic stenting had comparable short term efficacy, better quality of life, shorter hospital stay duration, lower cost, less frequent procedure-related complications, and lower 30-day mortality rate. However, endoscopic stenting was associated with higher recurrence biliary obstruction. This condition should be carefully appraised as some evidence regarding higher number recurrence biliary obstruction come from studies using plastic stent and not self-expandable metal stent (SEMS).[10,13,14]

In conclusion, ESGE recommend endoscopic stenting for malignant biliary drainage compared to surgery bypass.[12] Decision regarding endoscopic stenting or surgical bypass for palliative should be made case by case considering patient's condition such as in very

ill or low life expectancy patients, endoscopic stent strategy may be more appropriate.

There are two types of stent being used for endoscopic stenting that commonly used, plastic stent and SEMS. SEMS showed more benefits compared with plastic stent employment such as lower re-intervention rates, lower risk of stent dysfunction, lower cholangitis rate, and longer patient survival.[12] Plastic stent had higher occlusion rate due to smaller diameter. SEMS had larger diameter which may contributed to longer patency rate. However, ingrowth and outgrowth tumor risk become concerned issue regarding SEMS usage. Ingrowth was defined as a tumor grows between the mesh lines of the stent while outgrowth defined as tumor that blocked proximal or distal end of stent. Covered SEMS was invented in order to prevent ingrowth.[15,16] Recent meta-analysis showed that covered SEMS had similar stent failure and patient mortality rate compared with uncovered SEMS. Covered SEMS also had lower ingrowth tumor rate but higher rate of overgrowth tumor. Uncovered SEMS was associated with lower stent migration and sludge formation, this finding can be explained because uncovered SEMS will be buried inside the tumor. Main disadvantage of uncovered SEMS were that once occluded, it was impossible to change or remove once placed, also due to tumor ingrowth, early occlusion may occur.[17-19] As conclusion, the decision regarding the use of plastic, uncovered SEMS, and covered SEMS should be made individually based on patient's condition and endoscopist experience.

Percutaneous biliary drainage (PTBD)

PTBD is another alternative minimally invasive procedure to relieve malignant biliary obstruction. PTBD may be guided using fluoroscopy or combined ultrasound. PTBD can be performed when ERCP was failed due to failed papillary cannulation and endoscope cannot access the papilla due to obstruction which may occur in 5-10% of cases.[20,21] The main contraindication regarding PTBD procedure is uncorrectable bleeding diathesis. ESGE recommends stenting via ERCP over PTBD, in consideration with data from a national database which showed lower adverse event rate, shorter hospitalization day, and lower cost.[12] One meta-analysis showed that ERCP biliary drainage had higher infection rate due to possibility of incomplete biliary drainage and incision of duodenal papilla may damage regular structure of duodenal papilla that mainly prevent intestinal bacteria to enter biliary or pancreatic duct retrograde. PTBD is associated with higher tube dislocation, bleeding, and metastasis incidence.[22] Quality of life of the patient should also be considered as it may be affected due to carrying external drainage tube. Other thing to be considered was the location of obstruction. ERCP is the preferred method for distal biliary malignant obstruction compared to PTBD, however in proximal biliary obstruction cases, PTBD may be preferred in hilar isolation case.[21]

Endoscopic Ultrasonography-guided Biliary Drainage (EUS-BD)

In recent year, EUS-BD gain favor in term for biliary drainage, especially when ERCP failed. ERCP may failed due to variation of ampulla anatomy, obstructed lumen, ampullary neoplastic infiltration, and other condition.[20] Previously, PTBD is the alternative method in case of fail ERCP, but now studies showed superiority of EUS-BD over PTBD. EUS-BD eliminate the need of external drainage tube of PTBD, therefore may lessen patient discomfort due to external catheter. EUS-BD may be performed using intrahepatic and extrahepatic approach, or rendezvous technique (EUS-RV).[23-25] Published meta-analysis showed high EUS-BD success rate (87-94%) and low adverse event (16-29%).[25]

GASTRIC OUTLET OBSTRUCTION (GOO)

The extension of pancreatic adenocarcinoma may result in GOO condition due to direct tumor invasion which accounted for 15-25%. Early sign of GOO should be evaluated in every pancreatic cancer patient. Patient with GOO may present with non-bilious vomiting, nausea, anorexia, malnutrition, dehydration, and epigastric fullness. GOO is associated with decreased patient quality of life, therefore GOO should be adequately managed as part of palliative management in unresectable pancreatic cancer patient.[26] Surgical gastrojejunostomy or stent placement or feeding tube placement through

endoscopic may be needed to relieve symptom of GOO and provide nutrition for the patient.[27]

Duodenal stent placement using SEMS may provide access for oral nutrition, relief of mechanical obstruction, and in the end improving patient's quality of life. Complete stent expansion may be established within 24-48 hour after employment. Uncovered SEMS may be preferred due to less migration rate, however had higher obstruction due to tumor ingrowth. Success rate of stenting placement was reported up to 90% and clinically success more than 80% of cases.[28] Uemura et al. found that endoscopic duodenal stent in advanced pancreatic cancer had no significant difference in the technical and clinical success rate, adverse event, and survival duration compared to surgical gastrojejunostomy.[29]

EUS-guided gastrojejunostomy (EUS-GE) using lumen apposing metal stent (LAMS) nowadays become interesting alternative for malignant GOO management. There are three types of techniques of EUS-GE: direct EUS-GE technique, balloon-assisted EUS-GE, EUS-guided double balloon-occluded gastrojejunostomy bypass. EUS-GE is associated with high technical (90-92%), clinical (85-92%) success rates, and lower adverse event rates (12 vs 41%) compared to surgical laparoscopic gastrojejunostomy.[30-32]

PANCREATIC CANCER CACHEXIA

More than 80% of patient with pancreatic cancer suffer cachexia. More than 80% of pancreatic cancer patient had weight loss as presenting symptom at diagnosis and third of those patients had more than 10% of their initial weight. Many factors affect the nutrition status of pancreatic cancer patient such as progressive enlarged pancreatic mass may result in abdominal discomfort, nausea, vomiting, and early satiety; impairment of exocrine pancreatic function may result in steatorrhea and malabsorption syndrome while impairment of endocrine pancreatic function due to cancer may lead to diabetes mellitus.[33-35] Cytokine release by pancreatic cancer may result in hypercatabolic state which lead to increased nutrient consumption and also impair patient's appetite. Cancer cachexia is associated with poor prognosis, reduced quality of life, complication rate, longer hospital stay, and therapeutic response, while some studies showed weight stabilization may lead to better survival rate therefore prompt evaluation and comprehensive nutrition management are warranted for advanced pancreatic cancer.[33-36] Consultation with nutritionist may be needed to evaluate the degree of malnutrition and planning for nutritional therapy.

Patients with pancreatic cancer had higher risk for vitamin deficiencies which may be caused due to pancreatic enzymes insufficiency, resected bowel, or altered anatomy. Vitamin B12 deficiency may occur after gastric antrum resection which lead to decreased production of intrinsic factor. Vitamin B12 monthly injection may be needed.[35] Steatorrhea due to depressed pancreatic exocrine pancreas function may lead to malabsorption of lipid soluble vitamin such as vitamin A, D, E, and K. Resection of duodenum may lead to zinc and iron deficiency. Anemia in pancreatic cancer should be evaluated whether from iron deficiency or vitamin B12 deficiency, and the need for blood transfusion should be used judiciously. When sign of malabsorption occurred, adequate enzyme supplementation may be needed. Fulfilling calories needs should be adequately addressed with account for basic patient's nutritional demand and increased metabolic rate. Other adjuvant nutritional support such as fish oil containing omega-3, L-carnitine, leucine, and ketogenic diet still need further evaluation to become routinely advised.[35-37]

Route of nutritional support should be determined case by case. Enteral nutrition is the preferred method when no contraindication was present. Enteral nutrition was associated with reduced complication, hospital stay, improved mucosal gastrointestinal integrity, and nutritional status. Energy dense protein and calories, also oral nutritional support may be needed. Prevention and management of chemotherapy-induced nausea vomiting (CINV) should be employed as CINV may impair adequate nutritional intake of patient. Total parenteral nutrition (TPN) may be considered as short term supportive therapy in post-operative pancreatic cancer or physical obstruction and

severe anorexia. However, several issues related with TPN should be carefully addressed such as hyperglycemia risk, infection, cholestasis, and allergic reaction.[35,37,38]

PRURITUS OF CHOLESTASIS

Patient with pancreatic cancer may have complaints regarding pruritus. Pruritus is caused due to cholestasis due to obstructed bile duct caused by compression of pancreatic mass. Pruritus may present in mild to debilitating intensity which can lead to decreased quality of life and sleep deprivation.[39] The mechanism of pruritus development due to cholestasis is still unclear. Many hypotheses had been proposed regarding the pathophysiology of pruritus, however recent studies showed that accumulation of pruritogens was possibly the main mechanism. Many pruritogens such as bile salt, endogenous opioid, histamine, serotonin, progesterone and estrogen, and lysophosphatidic acid (LPA) are regarded as the putative pruritogens in cholestasis condition. Many studies showed that LPA is the closest candidate as the main putative pruritogens in cholestasis. LPA and autotoxin, enzyme that cleaves lysophospholipase to form LPA, are found elevated in cholestasis patient.[39-41]

Recommendations regarding management of cholestasis pruritus are mainly derived from cholestasis due to chronic liver disease studies. In term of obstructive cholestasis in advanced pancreatic cancer, relieve of obstruction become priority to reduce itchiness.[41] Many methods for relieving biliary obstruction have been described before in this text. American Association for The Study of Liver Disease (AASLD) and European Association for The Study of Liver Disease (EASL) recommend ursodeoxycholic acid (UDCA) only for intrahepatic cholestasis of pregnancy, because there are no evidence UDCA may improve pruritus relieve in other cholestatic condition. Antihistamine is also not recommended. Cholestyramine (4-16 gram/day), a bile acid resin, was recommended by AASLD and EASL as the first line treatment for cholestasis pruritus. Another recommended therapies in stepwise order by the guideline are rifampicin (150-300 mg), naltrexone (50 mg), sertraline (75-100 mg), and experimental approach (ultraviolet B phototherapy, plasmapheresis and other).[40,42]

CANCER PAIN

Studies showed 64% of patients with advanced cancer complaining about pain and up to 60% of patient on chemotherapy report pain.[43] Specific for pancreatic cancer patient, more than 50% of patients had major symptoms of abdominal and back pain. Pain may radiate from the abdominal area through the back area.[44] European Society of Medical Oncology in their latest guideline regarding management of cancer pain in adult patients stated that up to 44% pancreatic cancer had pain.[45] Pain may impair patient's quality of life, negatively affecting patient outcome, and increased psychological stress. Even after recognition of the negative contribution of cancer pain for patient overall health, studies showed that cancer pain is still undertreated. Several barriers had been identified such as lack of opioid access, clinician, patients, and regulatory barrier. Pain assessment should be employed regularly and recognized as the "fifth vital sign" in cancer patient especially in advanced cases of pancreatic cancer. Many tools can be used to assess pain such as visual analog scale (VAS), numerical rating scale (NRS), and verbal rating scale (VRS). Education regarding the important of pain diaries should be emphasized. Pain diaries should include frequency of medication use, time of day medications are used, side effects, and the effectiveness of pain medicine given.43,45 World Health Organization had issued recommendation that commonly termed as analgesic ladder. Mild pain (pain score 1-3) can be managed with paracetamol and non-steroidal anti-inflammatory drug (NSAID). ESMO recommends that the choice of initial analgesic should be based on WHO analgesic ladder severity level. ESMO also stated that currently there is no significant evidence to support or refute paracetamol and NSAID drug alone or in combination for mild to moderate pain.[45] Judicious use of paracetamol is warranted for advanced pancreatic cancer because commonly in those patients had already liver impairment. Adjuvant medication can be given such as antidepressants (duloxetine, tricyclic antidepressants) and anticonvulsants

(pregabalin, gabapentin). For moderate pain (pain score 4-6) may require weak opioid such as codeine or tramadol. For severe pain (pain score 7-10) usually requires strong opioids such as morphine, fentanyl, and oxycodone. Patient should be educated for taking high fiber intake to prevent constipation due to opioid side effect. Laxatives such as lactulose and bisacodyl can be given to treat constipation. If opioid failed to control the pain, several interventions may be needed such as epidural anesthesia, nerve block, surgical intervention, and radiotherapy especially for bone metastasis.[43-45]

CONCLUSION

Most of pancreatic cancer patients were diagnosed in late stage or unresectable condition. Palliative management usually become the best approach for the patient. A gastroentero-hepatologist should collaborate with other specialties to give comprehensive palliative care for advanced pancreatic cancer patients in order to improving their quality of life.

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