Review Article

Novel Treatment Strategies and Palliative Care in Pancreatic Cancer

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ABSTARCT

Pancreatic cancer is a form of aggressive cancer associated with low survival rate. The diagnosis of pancreatic cancer is always a challenge as the signs and symptoms associated with pancreatic cancer in most cases are non-specific. The only curative treatment of pancreatic cancer is through surgical approach. However, only 15% to 20% of patients are considered to be candidates for surgical resection. Despite 5-fluorouracil/leucovorin with irinotecan and oxaliplatin (FOLFIRINOX) and gemcitabine/nabpaclitaxel significantly improving outcomes for metastatic cancer, refractory disease still poses significant challenges. In addition, throughout the course of the disease, most patients suffer significant symptom burden and they will require palliative treatment designed to control the symptoms of unresectable or recurrent pancreatic cancer. In this review, we recapitulated the clinical presentation, risk factor, diagnosis, staging, pathology, general treatment and prognostic factors of pancreatic cancer. We also summarises the novel leading therapies in pancreatic cancers, focusing on passive and specific immunotherapies as well as ixabepilone, which are urgently needed to optimise the existing treatment of pancreatic cancer. Moreover, a critical presentation of palliative care, emphasising on the management of specific symptoms related to pancreatic cancer, is also offered. We stress on the importance of early institution of palliative care in the disease trajectory to improve symptom control, quality of life, patient and caregiver satisfaction, illness understanding, quality of end-of-life care as well as extend survival and reduce the costs of care.

Keywords: Pancreatic cancer, treatment, diagnostic strategy, patient care

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1. INTRODUCTION

Worldwide, around 338,000 people were estimated to have been diagnosed with pancreatic cancer in 2012. [1] While in Malaysia, pancreatic cancer is a rare form of cancer. Among the Malaysian population, the probability of developing the cancer for males is 0.2% whereas females exhibit a slightly higher risk of 1.3%. [2] From the latest update of Malaysian Cancer Registry's report, only 284 cases of pancreatic cancer were reported in year 2007 out of the total of 18,219 cancer cases. [2] Nevertheless, pancreatic cancer is a form of aggressive cancer associated with low survival rate. Early detection of this disease is nearly impossible as the symptoms are often vague and thus it is also known as the 'silent killer'.

1.1 Clinical presentation

The main presenting symptoms of the pancreatic cancer patients are pain, weight loss and jaundice. [3,4] Presence of pain before operation significantly predicts survival as Kelsen *et. al* found that the patients who had pain undergoing resection had a significantly better median survival compared to those without pain. [5] On the other hand, the obstructive jaundice often presents as mild but progressive pain in the abdomen which radiate to the back in approximately 25% of the patients and usually noted worse at the end of the day. [4,6] Other common symptoms include newly onset diabetes, fatigue and anorexia. [6,7] These symptoms typically appear unnoticed at an average of 4 months prior to the diagnosis of pancreatic cancer. [4]

1.2 Risk factor

The exact cause of pancreatic cancer is not known but research has identified a variety of risk factors. Cigarette smoking is the major culprit which accounts for approximately 25% to 30% of cases. [3] It is believed that the carcinogens from the tobacco smoke gain entry to the pancreas from the bloodstream after being

absorbed from the lungs. For dietary factor, it is less contributing to the pancreatic cancer but diet with high fat content which causes obesity is one of the suspected risk factors. In contrast, consumption of high fibres diet could prevent the cancer. [8] In addition, inherited germline mutation disorders such as the hereditary pancreatitis confer higher risk of developing pancreatic cancer. [8,9] The increase of the risk with decreasing time before the diagnosis of cancer may indicate that some of the patients are initially misdiagnosed as pancreatitis. [9] Pancreatic cancer also happens predominantly at old age. In United States, nearly half of the patients came from the age of more than 75 years old while only 13% of all the patients are diagnosed before 60 years old. [8]

1.3 Diagnostic strategy

The diagnosis of pancreatic cancer is always a challenge as the signs and symptoms associated with pancreatic cancer in most cases are non-specific. The lack of specificity for the diagnosis of pancreatic cancer when based on symptoms that are highly suggestive and sensitive for pancreatic cancer was shown in a landmark study in which 57% of such patients had other diagnoses, including non-pancreatic intra-abdominal cancers, pancreatitis, irritable bowel syndrome and other miscellaneous conditions. [10] Therefore, patients usually diagnosed at the later stage of the disease. In addition, a single diagnostic procedure is always not sufficient to provide a definitive diagnosis. Multidisciplinary diagnostic approach is used in the diagnosis of this disease.

1.3.1 Blood chemistry studies

There is no specific blood test for the diagnosis of pancreatic cancer. Full blood count may show anaemia and hypoalbuminemia. [11] Elevation of liver serum markers such as alkaline phosphatase, gamma-glutamyl transferase, bilirubin and aminotransferases levels may be seen in patients present with jaundice or obstructive bile duct. [12] However, metastasis to the liver in the absence of biliary obstruction may not always cause an increase in those markers. [11,12] Patient may also present with prolonged prothrombin time and impaired glucose tolerance. [11]

1.3.2 Role of tumour markers

Various serum biomarkers have been studied in related to pancreatic cancer such as carbohydrate antigen (CA) 19-9, 242, 50 and 125, and carcinoembryonic antigen. [13-15] However, none of these are specific to pancreatic cancer as their levels are also found to be elevated in other types of cancer and almost not applicable for early detection of pancreatic cancer. [16] CA 19-9 is the most commonly used tumour marker in the diagnostic staging as well as monitoring of treatment of pancreatic cancer as it has a significantly higher level of sensitivity compared to other tumor markers. [13,16] Moreover, CA 19-9 serum marker is also useful in predicting the resectability of pancreatic malignancy in suspected patients at laparascopic assessment and reduces unnecessary laporotomies in which 83.9% of the resectable tumors and 33.3% of the unresectable tumors were correctly identified in group of patients with high CA19-9 levels. [17] However, CA 19-9 has a lower specificity compared to CA 242. [16] As reported in one study, there was no elevation of CA 242 serum level in conditions such as cholestasis or acute pancreatitis but CA 19-9 was frequently elevated in patients with cancers other than pancreatic cancer and various benign pancreaticobiliary disorders. [16]

1.3.3 Ultrasonography (US)

Ultrasonography is often used as the initial imaging study in patients presenting with symptoms suggestive of pancreatic cancer because it offers rapid assessment of the pancreas and is non-invasive as well as cost-effective. [12,18] This imaging technique has a sensitivity of 95% in tumours larger than 3 cm. Although its sensitivity is much less in smaller tumours, it can be improved by the use of ultrasound contrast. It is also useful for differential diagnosis of pancreatic adenocarcinoma and inflammatory pancreatic masses. Even so, the assessment of local tumour spread is dependent upon the expertise of the operator. Local pancreatic tumour assessment could be challenging if the pancreas is covered with adipose tissues or bowel gas. Although there are reports implying that the sensitivity and specificity of ultrasonography are comparable to computed tomography, it is not true in most cases because ultrasound alone does not provide consistent accuracy for diagnosis and staging of pancreatic cancer and therefore a follow-up by other imaging modalities are needed. [18]

1.3.4 Computed tomography (CT)

CT is the most widely used imaging tool in the diagnosis and staging of pancreatic cancer. [18] Multidetector CT (MDCT) with enhanced

contrast is a CT-advanced technology having greater accuracy compared to the conventional CT. Pancreatic cancer enhances poorly compared to the surrounding pancreatic parenchyma in the early phase of dynamic CT and gradually enhances with delayed images. Therefore, hypoattenuated area on contrast-enhanced CT image is commonly regarded as pancreatic cancer. [12] MDCT is also able to detect local vascular invasion and local or distant tumor metastases with high sensitivities. [18] Triple-phase IV contrast MDCT scan, preceded by non-contrast CT, is a good technique for detecting and staging pancreatic neoplasms with a sensitivity of 89–97% and may detect masses less than 2 cm. [12]

The drawbacks of CT include exposure to radiation and risk of contrast-induced nephropathy. In inflammatory condition, CT may cause false positive result. [12] It is of utmost importance that MDCT performs prior to therapeutic stenting of biliary obstruction because it could interfere with the performance of MDCT. [18]

1.3.5 Endoscopic ultrasound (EUS)

Due to the small distance between the echoendoscope and the pancreas through the gastric or duodenal wall, transducers with high frequencies can be used, providing high resolution images and penetration depths ranging between 6 mm (20 MHz) and 3–4 cm (10 MHz). Therefore, EUS is said to be advantageous compared to US. [18] It has sensitivity of more than 90% in detection of pancreatic tumours as reported by many publications. [19] Diagnostic accuracy for pancreatic cancer in the EUS-guided fine needle aspiration (EUS-FNA) is also found to be superior over US- or CT-guided FNA. [19] However, inflammatory changes in the pancreas is hard to be differentiated from malignant masses due to similar appearance in EUS image. [18]

1.3.6 Endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP)

ERCP is used for visualisation of biliary tree and pancreatic duct. An alternative to diagnostic ERCP is MRCP. MRCP uses magnetic resonance technology to create a three-dimensional image. Both can serve as an alternative to EUS-FNA but with lower sensitivity. [20] Early meta-analysis data on sensitivity and specificity of ERCP in pancreas cancer diagnosis showing a result of 92 % and 96% respectively. [21] Meanwhile, MRCP was shown to be at least as sensitive as ERCP in detecting pancreatic cancers. [22] The advantage of MRCP over ERCP is that it allows evaluation of the biliary duct both above and below stricture and prevents potential complication of ERCP-induced pancreatitis. In addition, MRCP is also helpful in differentiating pancreatic cancer and chronic pancreatitis. [12]

1.3.7 Magnetic resonance imaging (MRI)

The signal-to-noise ratio and relatively slow speed of image acquisition as well as a large number of artefacts that produced with bowel movement indicate that MRI is not as valuable a tool as MDCT in the diagnosis of pancreatic cancer. Both availability and cost of MRI also further limiting its use as a diagnostic tool. Therefore, MRI is considered as additional diagnostic modality if prior MDCT imaging shows equivocal results include focal enlargement of the pancreas without definable mass or in patients with contraindications for iodine contrast administration. [18] Another potential benefit of MRI is its increased sensitivity for the detection of small liver metastases compared with CT. [23]

1.3.8 Positron emission tomography (PET)

PET is a non-invasive diagnostic modality. The only positron-emitting radiopharmaceutical tracer allowed by the US Food and Drug Administration (FDA) is fluorine-18 fluorodeoxyglucose, a glucose analogue which could give false negative result in patients with hyperglycaemia. [18] The sensitivity of PET for detecting pancreatic cancers ranges from 71% to 92% with specificities between 64% and 94%. [24-26] However, false positive results can be seen in patients with various pancreatic inflammatory diseases. [24] PET did not provide any additional information in patients with equivocal CT findings but may be complementary to CT and MRI in patients with pancreatic carcinoma in the search for distant metastases. [18]

1.3.9 Biopsy

Biopsy is indicated in patients with unresectable pancreatic mass on imaging before initiating chemotherapy or radiotherapy. It should also be done in patients with suspected rare malignancies and having history of other malignancies because appropriate treatment for metastatic disease to the pancreas may be non-operative management. [27] Tissue for histological or cytological assessment is

commonly obtained through FNA technique. Currently, this technique is guided by imaging modalities such as EUS. The sensitivity and specificity of FNA are dependent upon the size of the tumour. [27] A meta-analysis of 15 studies with 1860 patients found that overall, the sensitivity of EUS-FNA for pancreatic cancer was 92%, and the specificity was 96%. [28] However, FNA technique may cause complications such as pain, fever, pancreatitis duodenal perforation, retroperitoneal bleeding and abscess. [29]

1.3.10 Laparoscopy

Laparoscopy is used in determining resectability of pancreatic tumour but it remains controversial as there is not enough evidence to include them in the staging algorithm. Patient selection for preoperative laparascopy needs to be done carefully. In a population-based study, the authors conclude that the surgeons opt for laparascopic assessment when the patient are highly suspected with unresectable disease. [30] Another limitation of this method include the incompetency in the assessment of vascular invasion, lymph node involvement and deep hepatic metastases. [30]

1.4 Staging

The main system used to stage pancreatic cancer is the tumour-node-metastasis (TNM) system by combined American Joint Committee on Cancer/International Union Against Cancer. This system utilises 3 parameters which are T, N and M (**Table 1**). [31] T indicates the primary tumour size and if it has grown outside the pancreas and into surrounding organs. N indicates if the tumour has spread to regional lymph nodes and M describes if the cancer has metastasized to other organs of the body. After the categories T, N and M have been determined, the information is combined to assign an overall stage of 0, I, II, III and IV. This process is known as stage grouping (**Table 2**). [31]

Table 1. TNM classification for pancreatic cancer [28]

Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour limited to the pancreas, 2 cm or less in greatest dimension
T2	Tumour limited to the pancreas, more than 2 cm in greatest dimension
T3	Tumour extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumour involves the celiac axis or the superior mesenteric artery (unresectable primary tumour)
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Table 2. Stage grouping of pancreatic cancer [28]

Stage 0	**Tis**	**N0**	**M0**
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

At Stage 0, the tumour has not invaded the deeper tissues and is located at the top layers of pancreatic duct cells. [31] While at stage I, the cancer has formed and is found in the pancreas only. This stage is further divided into stage IA, where the tumour is 2 cm or smaller and stage IB, where the tumour is larger than 2 cm. At stage II, the cancer may have spread to nearby organs and tissue, and also lymph nodes near the pancreas. Stage II is divided into stage IIA and

stage IIB. Stage IIA indicates that the cancer has spread to nearby tissue and organs but has not spread to nearby lymph nodes while in stage IIB, the cancer has spread to nearby lymph nodes in addition to nearby tissue and organs. In stage III, the cancer has spread to nearby major blood vessels and nerves near the pancreas. The cancer also may have spread to nearby lymph nodes. As for the final stage, stage IV, the cancer can be of any size and it has spread to distant organs such as the liver, lungs and peritoneal cavity. [32]

1.5 Pathology

The most common exocrine pancreatic tumours are ductal adenocarcinoma which accounts for well over 90% of all tumours. [3] The majority of ductal adenocarcinomas area consists of gritty, hard, scirrhous, grey-white masses that are poorly circumscribed due to invasion of the adjacent pancreas or nearby tissues. The designation as "ductal" does not necessarily imply origin in the main pancreatic duct or major branch ducts. However, it appears to arise more peripherally in small ducts within the acinar tissues. As they grow, pancreatic ductal neoplasms can cause obstruction of pancreatic duct and lead to chronic pancreatitis in the obstructed segment of the pancreas. Steatorrhea and malabsorption are usually not a clinical problem as the accessory duct of Santorini can allow bypass of the main pancreatic duct. [33]

Most pancreatic ductal adenocarcinomas are moderately to poorly differentiated having varying degrees of duct-like structures and mucin production. Histologic grading uses three grade levels based on the degree of differentiation and the prevalence of mitotic cells. Ductal adenocarcinomas tend to have dense stromal fibrosis. Therefore, they are referred to as "scirrhous" or "desmoplastic" carcinomas. The stromal fibrosis is attributed to alterations in transforming growth factor-beta signalling. [33]

1.6 Treatment

There are five types of standard treatments used for treating pancreatic cancer, namely surgery, radiation therapy, chemotherapy, chemoradiation therapy and targeted therapy. The only curative treatment of pancreatic cancer is through surgical approach. Localised tumors are categorized on a continuum from "resectable" to "unresectable (locally advanced)" according to the involvement of the local vessels and it is recommended to refer to the National Comprehensive Cancer Network criteria for resectability/irresectability. [34] After careful assessment, only 15% to 20% of patients are considered to be candidates for surgical resection because of the late presentation of the disease, and many of these patients are found to have microscopically positive margins at the time of surgery which strongly predicts early recurrence and short survival. [35] If the tumor is deemed not resectable, the aim of treatment is prolongation of survival and palliation of symptoms related to the disease by optimal local control and control of metastatic growth. [34]

One of the types of surgery that can be performed to remove the tumour would be the Whipple procedure. In this procedure, the gallbladder, head of the pancreas, part of the stomach and part of the small intestine and bile duct are removed. The remaining pancreas is enough to produce digestive juices and insulin. Another type of surgery would be total pancreatectomy which removes the entire pancreas as well as part of the stomach, gall bladder, small intestine, spleen and nearby lymph nodes. The last type of surgery would be distal pancreatectomy in which the spleen and the body and tail of pancreas are removed. [32]

Radiation therapy comes in two forms, namely external and internal radiation therapies. The external radiation therapy utilises a radiation from a machine outside of the body to kill the cancer cells. The internal radiation therapy on the other hand, employs a radioactive substance sealed in needles or catheters that are placed directly into or near the cancer. In order to decide which therapy to use, stage of the pancreatic cancer being treated must be considered. [32]

Chemotherapy is a type of cancer treatment that utilises anticancer drug to stop the proliferation of cancer cells, either by killing the cells or by inhibiting their division. Usually, the treatment is given in the form of combination chemotherapy where more than one anticancer drugs are administered to the patient. The choice of the drugs used for chemotherapy also depends on the stage of the pancreatic cancer being treated. [32]

Meanwhile, the chemoradiation therapy involves combination of chemotherapy and radiation therapy which could increase the effects of both. Lastly, the targeted therapy utilises drugs or other substances that identify and attack targeted cancer cells without harming the normal cells. An example of a class of drugs utilised in this type of therapy would be the

tyrosine kinase inhibitors (TKIs) which block the signals needed for tumour growth. Erlotinib is one of the TKIs used to treat pancreatic cancer. [32]

The treatment for pancreatic cancer differs according to the stage of cancer. For stage I, the standard treatment option is radical pancreatic resection. For patients with pancreatic head tumours, it is recommended to have a pylorus-preserving pancreaticoduodenectomy by a modified Whipple procedure which preserves the distal stomach and pylorus. [34] As for tumours found in pancreatic body and tail, it is recommended to have distal pancreatectomy which also routinely includes splenectomy. [31] Postoperatively, 6 months of gemcitabine (GEM) or 5-fluorouracil (5-FU) chemotherapy are recommended. [34] It was reported that there were no substantial differences in terms of disease-free survival or overall survival in the comparison between 5-FU and GEM as adjuvant therapy in pancreatic adenocarcinoma. [36] A meta-analysis reported that 5-FU-based chemoradiation following GEM chemotherapy may be an option for individual clinical use, especially in patients with tumours of the pancreatic head, large tumour diameter (>3 cm) and in patients with R1 resection. [37]

Most patients with stage IIA pancreatic cancer who are having tumours that are unresectable should undergo palliative bypass of intestinal obstruction, followed by chemotherapy or chemoradiation. Nevertheless, when feasible, pancreatectomy can be considered a standard approach. A study showed that intraoperative radiotherapy (IORT) was associated with improved local control and overall survival, especially in patients with a lower trend to systemic disease spread. [39] Indications for adjuvant chemotherapy or in combination with radiation therapy is similar to stage I. [38]

However, for patients in stage IIB and III, the tumours usually encase blood vessels. Therefore, patients who have borderline resectable disease can be recommended to have preoperative therapy, which consists of chemoradiation or induction chemotherapy followed by chemoradiation to achieve downsizing of the tumour and may convert the tumour to become resectable. However, the optimal neoadjuvant strategy is still under investigation and there is so far no standard protocol exist to guide neoadjuvant chemoradiotherapy. [34] For patients that have unresectable disease, the 5-FU-based chemoradiation can be recommended. [38] This suggestion is based on a retrospective analysis of patients enrolled in the GERCOR studies in which patients treated with GEM not progressing after 3 months of treatment and with a good performance status achieved an improvement in survival with the addition of chemoradiation although these data have to be confirmed in a prospective trial. [40]

Treatment with GEM is a reasonable choice for patients with stage IV pancreatic cancer and was the standard chemotherapy until recently. [34] A meta-analysis reported that patients receiving GEM have a median survival of 6.2 months and a 1-year survival rate of 20%. [41] The use of a combination of GEM and other cytotoxic agents, such as 5-FU, irinotecan, cisplatin and oxaliplatin do not confer a major advantage in survival even in large randomised phase III trials and should not be used as standard first line treatment of locally advanced or metastatic pancreatic cancer. [34] Superiority for GEM combination is best documented for nabpaclitaxel [42] plus gemcitabine in which this combined therapy was associated with significantly higher objective response rate and significantly longer median overall and progression-free survival. [43] Another therapeutic possibility is a combination of GEM and erlotinib on the basis of a randomised trial from the NCI of Canada. [44] However, the very modest survival gain (~2 weeks) and the high economic costs of the treatment question the role of combination of GEM and erlotinib in metastatic pancreatic cancer. [34] As only patients who exhibit a significant skin rash within 8 weeks of treatment appear to benefit from this combination, patients with metastatic pancreatic cancer can be treated with a combination of GEM and erlotinib, but treatment with erlotinib is only continued if patients develop skin rash within the first 8 weeks of treatment. [44] A combination of 5-FU, irinotecan and oxaliplatin (FOLFIRINOX) is now favoured over gemcitabine or a gemcitabine-based doublet for standard therapy of patients with metastatic pancreatic cancer who have a good ECOG performance status (0 or 1) and a serum total bilirubin level that is <1.5 times the upper limit of normal. [34] This recommendation is based on a phase III trial which reported that the objective response rate was significantly higher with FOLFIRINOX as was median progression-free survival and overall survival compared to gemcitabine monotherapy. [45]

Currently, there is no firmly established standard chemotherapy for patients after progression on first-line treatment. [34] The combination of 5-FU and oxaliplatin has been shown to confer a benefit in the second line setting after first line GEM in a small clinical trial and can be considered as a treatment option in this setting. [46] In patients treated with first-line FOLFIRINOX who can receive second-line chemotherapy after progression, GEM can be considered as an option. [34]

Patients should be followed at each cycle of chemotherapy for toxicity and evaluated for response to chemotherapy every 2 months. [34] Clinical benefit and tools such as CA 19.9 can be used to assess the course of disease in the metastatic setting and imaging procedures such as CT scan can be used to rule out the presence of metastases and to add radiotherapy to the treatment plan as well as ultrasound to monitor for the presence of ascites that can indicate peritoneal disease. There is no possibility of cure, even for recurrences diagnosed early and therefore, a follow-up schedule should be discussed with the patient and designed to avoid emotional stress and economic burden for the patient. [34,38]

2. Novel therapy

2.1 Immunotherapy

In pancreatic adenocarcinoma, interactions between tumour and host cells are mediated by inflammatory cells, fibroblasts and vascular endothelial cells. [47] The aggressiveness and chemo-resistance related to pancreatic cancer are often attributed to the immunosuppressive signals sent from pancreatic cancer cells to produce an immunosuppressive tumour microenvironment and the subsequent inflammation promotes formation of early, premalignant lesions and their progression. [48-50] The tumour microenvironment in pancreatic cancer preferentially favours the recruitment of immune suppressor, rather than immune effector, cell types. [51] Furthermore, a direct link is established between the prognosis of pancreatic cancer with the induction of a humoral response to the cancer antigens MUC-1 and mesothelin and the presence of intratumoural cytotoxic T lymphocytes and helper T cells. Based on these premises, both macrophage and cytotoxic T-lymphocyte targeted therapies in trials have the ultimate goal set on augmenting the antitumour immune recognition of pancreatic cancer. [48]

2.1.1 Macrophage-targeted therapy

Tumour-associated macrophages (TAMs) play a crucial role in the pancreatic ductal carcinoma tumour progression by promoting angiogenesis and metastasis, suppressing anti-tumorigenic immune response and possibly causing chemotherapy resistance and emergence of cancer stem-like cells. Thus, inhibition of macrophage recruitment to the site of tumour formation resulted in an elevated anti-tumour immune response in pancreatic cancer, as suggested by a significant increase in $CD8^+$ T cells, reduced $FoxP3^+$ T-reg infiltration and tumour progression when chemokine (C-C motif) receptor 2 or colony-stimulating factor 1 receptor inhibitors which suppress inhibitory TAM are used in combination with gemcitabine compared to single agent gemcitabine. [52] This promising result of the preliminary data warrants further research on targeting the TAM component of the tumour microenvironment. Nevertheless, since TAM may manifest both pro- and anti-tumour effects, a productive macrophage-directed immunotherapy needs to induce anti-stroma and anticancer activity. [48]

2.1.2 Cytotoxic T-lymphocytes-targeted therapy

An immunoreactive environment may be induced by stimulating endogenous $CD8^+$ T cells via interferon, adoptive T cell therapy, immune check point inhibitors and cancer vaccine.

2.1.2.1 Interferon (IFN)

Both type I IFN-α and -β were demonstrated to inhibit pancreatic cancer cell growth by inducing apoptosis and cell-cycle arrest, besides modulating the host tumour response by increasing nitric oxide production. [48] However, the clinical role of IFN-α remains conflicting. Picozzi *et al*. initially reported that 43 patients treated with adjuvant 5-FU, cisplatin, and IFN-α2b plus radiotherapy followed by adjuvant 5-FU in patients with resected pancreatic adenocarcinoma after a median follow up of 45 months showed median disease-free survival of 22 months, median overall survival of 42 months, with 5- and 10-year overall survival rates of 42% and 28%, respectively. [53] However, a randomized Phase III study comparing adjuvant chemoradiation plus IFN-α2b with 5-FU/leucovorin noted no significant survival difference, but significantly higher toxicities. [54] In another study, a survivin-derived peptide (AYACNTSTL) was used in combination with IFN-α to vaccinate 6 patients with advanced

pancreatic cancer. More than half of the patients had manifested immunological responses to vaccination, which were often accompanied by clinical benefits. IFN- α was thought to enhance the immunological responses of these patients. [55]

2.1.2.2 Adoptive T cell therapy

This immunotherapy which utilises the patient's own T-cells expanded and stimulated ex vivo allows manipulation of the T cells, such as priming of the cells to tumour antigens or transfection with recombinant DNA encoding for T cell receptors specifically directed towards tumour antigens. [48,56] IL-2 and CD3-specific antibody are used for stimulation and expansion of the autologous tumour-reactive T cells. This therapy depends on the ability to optimally select or genetically engineer cells with targeted antigen specificity and then to induce the cell proliferation while preserving their effector function and engraftment as well as homing abilities. Currently, there are no FDA-approved adoptive T cell therapy protocols for cancer. [57] However, pilot data with cytokine-induced T cells showed safety and median progression-free survival rates of 11 weeks and median overall survival of 27 weeks, comparable with second-line chemotherapy regimens in refractory pancreatic cancer patients. [58] Similarly, in another clinical study, mucin-1-specific autologous T cells, isolated from patient's peripheral blood mononuclear cells (PBMCs), were expanded by incubation with a mucin-1-presenting cell line prior to administration to pancreatic cancer patients. The mean survival time for unresectable patients in this study was 5 months. However, patients with resectable pancreatic cancer had 1-, 2- and 3-year survival rates of 83.3%, 32.4% and 19.4% respectively, and a mean survival time of 17.8 months. [59] In a similar study by the same group, adherent cells were isolated from patient PBMCs to generate mature dendritic cells (DCs) that were then pulsed with mucin-1 peptide. The pulsed DCs were administered, along with autologous expanded mucin-1-specific T cells, to patients with unresectable or recurrent pancreatic cancer. [60] Remarkably, a complete response was observed in one patient with lung metastases and the mean survival time of the whole group was 9.8 months, suggesting that the addition of pulsed DCs may have improved the outcome. In addition, the genetically engineered T cells to target tumours expressing prostate stem cell antigen, a tumour-associated antigen (TAA) frequently expressed by pancreatic cancer cells may also represent a promising novel treatment for patients with pancreatic cancer. [61]

2.1.2.3 Immune checkpoint inhibitor

Immunotherapy of pancreatic cancer will greatly benefit from the identification of pancreatic cancer-specific TAAs. However, cancer cells often exploit immune checkpoints to evade detection by cytotoxic T cells. [62] This rationalises the use of immune checkpoint inhibitors in pancreatic cancer. Management of pancreatic cancer with checkpoint blockade inhibitors monotherapy such as programmed cell death ligand-1 and cytotoxic T-lymphocyte-associated protein inhibitors lack significant activity probably due to reduced pancreatic cancer neoantigenic potential and the fact that pancreatic cancer elicits limited adaptive immune responses secondary to a high degree of immunological tolerance at baseline. [48,62] Indeed, the efficiency of immune checkpoint-targeting agents is dependent on adaptive immune responses. [62] However, combination therapy with vaccines, agents targeting other immunosuppressive cell population, chemotherapy or radiotherapy are currently being pursued. [48] The combination immune checkpoint blockers with anticancer vaccines particularly, could result in the elicitation of robust antigen-specific adaptive immune responses. This notion is supported by the results of a recent clinical study which favoured the combination of cytotoxic T-lymphocyte-associated protein antibody, ipilimumab and GVAX as compared with ipilimumab alone in previously treated locally advanced or metastatic pancreatic cancer patients. [63] Anti-programmed cell death ligand-1 antibodies such as BMS-936559 are also being utilised in clinical study. In the BMS-936559 study, 14 patients with pancreatic cancer were treated on this trial, but none of these patients demonstrated a clinical response. [64] Based on the clinical experience of using ipilimumab as combination therapy, anti-programmed cell death ligand-1 antibodies would most likely better succeed in a combinatorial approach for pancreatic cancer.

2.1.2.4 Cancer vaccines

Through the stimulation and maturation of dendritic cells for tumour-specific antigen presentation, cancer vaccines ultimately aims to activate the adaptive immune response with effective cytotoxic T lymphocytes. [48] Whole

cell vaccine is the simplest approach used in cancer by inoculating individuals with irradiated tumour cells which serves as immunogens. [50,65] The advantage of using whole-cell vaccines is that tumour cells express a wide range of tumour-associated antigens which could avoid the difficulty of picking the optimal tumour antigen to target for immunotherapy. [47,66] This rich source of antigens contains epitopes of the two types of T cells ($CD8^+$ and $CD4^+$), compared with peptide-based vaccines that contain only one epitope. Autologous tumour cells are the best source of protein for immunization, but it is difficult to prepare a sufficient quantity of tumour cells required to achieve the vaccine due to prolonged culture periods and possible contamination with bacteria and fungus. To avoid these difficulties, allogeneic tumour cells can be used, which can be produced in larger quantities and do not require determination of the patient's human leukocyte antigen and cell types. [47] Examples of whole cell vaccines include Algenpantucel-L, GVAX pancreas and IMM-101 vaccines. Algenpantucel-L is an irradiated combination of two human allogeneic pancreatic cancer cell lines. [48] Adjuvant algenpantucel-L with GEM and 5-FU based chemoradiotherapy after surgery for pancreatic cancer patients was shown to be well tolerated in a phase II study. The 1-year survival and the 1-year disease-free survival were 86% and 62% respectively. [67] The GVAX pancreas vaccine is another allogeneic whole cell vaccine transfected with granulocyte-macrophage colony-stimulating factor which acts as a maturation factor for the antigen presenting cells/DCs. [48] GVAX vaccine has been studied with chemoradiotherapy after resection of pancreatic cancer, and showed modest median disease-free and overall survival rates of 17.3 and 24.8 months respectively. The effect was attributed to the induction of $CD8^+$ mesothelin-specific T cells. [68] Mesothelin is a tumour-associated antigen that is overexpressed in most ductal adenocarcinomas of the pancreas and is thought to be involved in cell adhesion, and therefore, to play a role in metastasis. [47] The pancreatic GVAX vaccine has also been evaluated in patients with metastatic pancreatic cancer. [69] Two patient cohorts were enrolled in this open-label Phase II study: cohort A, including 30 patients who received a maximum of 6 doses of GVAX at 21-day intervals; and cohort B, including 20 patients who were treated with intravenous cyclophosphamide at a low dose (250 mg/m^2) to inhibit regulatory T cells (one day prior to the administration of GVAX). The median survival of cohort A and cohort B was 2.3 and 4.7 months respectively. [69] As mentioned beforehand, GVAX pancreas has also been combined with ipilimumab in a randomized study and it was reported that for patients with previously treated locally advanced or metastatic pancreatic cancer, overall survival rates were longer compared to ipilimumab alone. [63] On the other hand, Dalgleish *et al*. reported that IMM-101, a heat-killed whole cell vaccine of *Mycobacterium obuense* was able to induce a systemic immune response when combined with gemcitabine in 110 untreated patients with advanced pancreatic cancer, and observed overall survival of 7.2 months relative to 5.6 months with gemcitabine alone. [48]

Peptide vaccines are preparations of antigenic protein fragments that represent the minimal immunogenic region of TAA capable of activating a CD4/CD8 response. [48,70] A number of peptide vaccines especially the mutant KRAS peptide vaccine have been successfully used to produce antigen-specific responses in pancreatic cancer patients. It was found that after surgical resection of pancreatic cancer, mutant KRAS peptide vaccines conferred average survival rates of 27 months, and 5-year survival rates of 20%, comparable with historical adjuvant chemotherapy data. [48] Synthetic K-ras vaccines based on long peptides were also employed in a clinical study in a group of patients after pancreatic tumour resection to induce antigen-specific polyclonal $CD8^+$ and $CD4^+$ T-cells and reported a 10-year survival rate of 20%. [71] Nevertheless, the use of peptide vaccines has some drawbacks: the existence of a limited number of known antigenic peptides; the presence of suppressive immune cells in tumoural microenvironments; the fact that dendritic cells may have poor functionality in patients with advanced pancreatic tumours; the observation that $CD8^+$ cytotoxic T cells are sometimes ineffective in the reaction with pancreatic tumour cells, which is mediated by production of immunosuppressive cytokines such as interleukin-10 and tumour growth factor. [48]

DNA vaccines are only applicable with known specific tumour antigens. [65] A DNA vaccine is composed of a plasmid DNA that encodes for a TAA under the control of a mammalian promoter

and can be easily produced in the bacteria. [57] Regardless of the recipient's major histocompatibility complex profile, this technique which is administered via intramuscular injection with or without electroporation allows an immune response to multiple potential epitopes within an antigen. [65] DNA vaccines are stable and safe as mutations caused by putative integration events are extremely rare and do not possess viral proteins that may down regulate the immune system or elicit neutralizing antibodies. [51] Compared with cell-based vaccines, this vaccination strategy offers prolonged antigen expression, leading to amplification of immune responses and inducing memory responses against weakly immunogenic TAAs. [57] DNA vaccines are mainly applied to murine models of cancer in pancreatic cancer studies. [65]

2.2 Ixabepilone

Ixabepilone, a semisynthetic epothilone B analogue which promotes tumour cell death by stabilising microtubules and inducing apoptosis has a limited but promising data in the management of pancreatic adenocarcinoma as demonstrated in early phase clinical trials. [72,73] It retains antineoplastic activity against cancers that are naturally insensitive to taxanes or that have become taxane-resistant due to different binding mechanisms on β-tubulin and structural differences between these two classes of agents. [72,74]

3. Palliative care

Palliative care aims to improve the quality of life of cancer patients and their families by providing support with symptomatic relief, advance care planning as well as psychological support and education. Since the past few decades, palliative care is no longer only the end-of-life treatment but rather a supportive care delivered to patients with life-limiting disease. [75] American Society of Clinical Oncology in its provisional clinical opinion recommended the early initiation of palliative care in conjunction with standard oncology care for patients with cancer which limits the prognosis of the patients. [76,77] Multiple studies have shown that early palliative care in the disease trajectory can improve symptom control, quality of life, patient and caregiver satisfaction, illness understanding, quality of end-of-life care as well as extend survival and reduce the costs of care. [75,78] Bakitas *et al*. also reported that early palliative care results in significant improvements on family members' depression. [76,79] Therefore, early palliative care is not only beneficial for patients but also their families.

3.1 Perspective of patients

In palliative care, patients should not be treated as an illness but as a complete human with physical, psychological, social and spiritual needs. [77] Therefore, a good palliative care services provide not only physical care but also psychological, social and spiritual support.

3.1.1 Psychological perspective

Development of psychological and psychiatric symptoms can be seen in most patients after knowing the diagnosis of cancer. Similar psychological and psychiatric complications can also occur at each transitional point of cancer, such as treatment initiation, disease progression, recurrence, and treatment failure. [80] Most of them experience emotional impacts such as shock, denial, anger, anxiety and depression. [80,81] The percentage of anxiety varied from 0.9% up to 49% in emotional distressed cancer patients. Insomnia, shortness of breath, numbness, tension, worry and restlessness are some of the symptoms that can be observed in patients with anxiety disorders. Meanwhile, clinically significant depression occurs in approximately 25% of patients with advanced disease. [81] The life-threatening diagnosis, side effects from pharmacological treatment, loss of independence and functionality, poorly controlled symptoms and poor communication with healthcare providers are some reasons for depression in cancer patients. [82]

Emotional distress can also happen if patients focus on their regretted actions, unfulfilled ambition, and loss of role in occupation, social and family. The feeling of themselves as a burden for family and the fearing of death and leaving their loved ones are also sources of emotional distress in cancer patients. [80] The mental adjustment of cancer patients is correlated with psychological distress. The most adaptive psychological adjustment among the others is 'fighting spirit' and the most maladaptive among the others is 'helplessness or hopelessness'. [83]

3.1.2 Social perspective

Cancer patients' dependence on others, changes in their role in family, isolation, loss of job and frequent meeting with healthcare team are some common social changes that may occur in cancer patients. [84] This is because the associated physical issues of cancer such as physical disability, fatigue and pain limit their ability to

perform daily routine activities such as bathing, preparing and eating meals. They are unable to go to school or continue their work, which in turn will affect their social roles and reduce their income and financial problems. Financial stress occurs when patients are unable to work during treatment, loss their employment and income or lack of health insurances. It was reported that patients living with chronic illnesses face inability to pay their medical bills or inability to cover their living expenses due to medical debt. [85] Emotional support from physicians is the most effective social support which is extremely beneficial to cancer patients in helping them to cope better with cancer, especially in patients' mental adjustment. Yet, cancer patients often complain their psychosocial needs are not well addressed by their healthcare providers. [84]

3.1.3 Spiritual perspective

Spirituality can be defined as "an individual's relationship to and experience of transcendence or the individual's sense of peace, purpose, and interconnectedness, including beliefs about the meaning of life". [87] The feeling of safety and secure is one of the main spiritual needs in patients.[86] Patients' spiritual needs can also be classified into religious needs, existential needs, search attention, search inner peace and actively connecting, the need to complete their targeted tasks, preparation for death, and the need for "positive outlook". [86] Most people wish to search for the meaning and purpose of life, especially when being diagnosed with incurable life-threatening cancer, related to death. Cancer patients often question about why they are the chosen ones, where they will go after death, and what is their purpose to this world. The majority of patients with chronic life-threatening disease wish their spiritual issues to be addressed in their care. [87] The spiritual relationship to God from patient's perspective can compensate their unexpressed needs. [86] God can become patients' personal addressee, who can understand and accept patient's distress hopes and sorrows. Thus, 'internal dialogue' such as prayers and verbalisation of needs can help patients feel better. [87] Regardless of the religions or beliefs patients are following, positive and open-minded spiritual thoughts always bring patients to accept their condition better and help to let go of negative thinking.

3.2 Management of specific symptoms

Throughout the course of the disease, most patients suffer significant symptom burden and they are frequent users of the emergency department. Typical patients will require numerous interventions targeting multiple issues as followed.

3.2.1 Biliary Obstruction

Approximately 70-90% of patients with pancreatic cancer develop biliary obstruction, resulting in jaundice, pruritus, coagulopathy, and liver failure. [88,89] The surgical options for achieving biliary decompression include an anastomosis between the gallbladder and jejunum (cholecystojejunostomy) or common bile duct and jejunum (choledochojejunostomy). [89-92] Drainage is successful in returning the serum bilirubin concentration in approximately 90% of patients; in the remainder, persistent hyperbilirubinemia may be seen due impaired hepatic function. [90] However, endoscopic biliary stent placement remains the mainstay for the palliation treatment of biliary obstruction. A meta-analysis reported no difference in survival between endoscopic stent placement and surgical bypass for malignant obstructive jaundice but endoscopic stent placement is associated with lower morbidity and procedure-related mortality although stented patients have more frequent readmissions for stent occlusion, recurrent jaundice, and cholangitis. [93,94] Endoscopic biliary stent placement is technically successful in more than 90% of attempted cases.[95] Self-expandable metallic stent is preferred over plastic biliary stent as it has longer patency. [96] Plastic stent, with a median patency of 2.5 months, require replacement every 3 months. Furthermore, metallic stent has lower occlusion rate compared with plastic stent. [97] Long-term complications such as cholangitis occurs in 30% of patients with biliary stents and it is treated with antibiotics and emergent stent change to prevent sepsis and hepatic abscess formation. [88]

3.2.2 Weight loss

Weight loss is observed in many pancreatic cancer patients. It may be due to systemic cachexia caused by tumour growth, nutritional deficiencies caused by pancreatic exocrine insuffiency or reduced food intake. [98,99] Nutritional support has been practiced to limit weight loss and improve quality of life.

3.2.3 Pancreatic insufficiency

Pancreatic exocrine insufficiency occurs in 80% to 90% of patients with pancreatic cancer. [88] It is defined as inadequate pancreatic enzyme activity for digestion, resulting from pancreatic

duct obstruction, pancreatic resection, gland fibrosis, or atrophy. [97,100] Patient with pancreatic exocrine insufficiency will develop fat and protein malabsorption, manifests as bloating, excessive flatus, diarrhoea, and steatorrhea. Untreated malabsorption may contribute to nutritional deficiencies and weight loss. [97,101] Pancreatic enzyme replacement therapy (PERT) is indicated for progressive weight loss and steatorrhea. PERT is usually started at 50,000 International Unit (IU) pancreatic lipase with each full meal and one half of the dose with snacks before titrating the dosage according to symptoms to ameliorate gastrointestinal side effects associated with the therapy. [100,102-104] Use of enzyme supplements was associated with improved weight gain and decreased fat and protein malabsorption. [105] Several commercial preparations consist of acid-resistant and pH-sensitive microspheres which are designed to be acid-resistant thus avoiding enzyme inactivation by gastric juice and releasing lipase at a pH of 5.5-6, assumed to be in the duodenum. [97,102,105] In a small randomised trial, enteric-coated enzyme supplements resulted in higher body weight gain than did non-enteric coated supplements following pancreaticoduodenectomy. [106] Addition of proton-pump inhibitors optimizes PERT by increasing intestinal pH to reduce inactivation of prescribed PERT. [102] Failure of PERT to return fat digestion to normal could be due to underdosing of enzymes and intestinal bacterial overgrowth. [107,108]

3.2.4 Cachexia

Cachexia is a complex metabolic syndrome characterised by progressive weight loss and muscle wasting resulting from an increased catabolic rate. [88,109] It is observed in 80% of pancreatic cancer patients at the time of diagnosis. [88] Cachexia is mediated by the release of proinflammatory cytokines and other factors secreted by tumour, including tumour necrosis factor-alpha (TNF-α), interleukin-1-beta, interleukin-6, ciliary neurotropic factor and the proteolysis-inducing factor. [103] Supportive nutrition with oral caloric supplementation is used to manage cachexia. Progestational agents and corticosteroids such as megesterol acetate, medroxyprogesterone acetate, and dexamethasone have been shown to improve appetite and increases weight in patients with cancer. [103,110] Eicosapentanoic acid helps pancreatic cancer patients to gain weight by suppressing the effect of proteolysis-inducing factor. [111] Thalidomide reduces weight loss by reducing the production of the TNF-α. [88,103] However, this drug has not been approved by FDA for this indication. [88,103]

3.2.5 Pain

Pain is one of the most frequently reported symptoms in pancreatic cancer patients in which 70% to 80% of them experience substantial pain. [112] Proximity of pancreas to other organs such as liver, stomach, duodenum, jejunum and transverse colon is one of the reasons that pain is frequently experienced by pancreatic cancer patients. [6,110] Patients may perceive pain at multiple and distant sites with progressive nature as the disease worsens. Midepigastric pain is thought to arise from the body of the pancreas which appears as midepigastric discomfort, while pain originating from the tail of the pancreas is often located at the left epigastrium and left intercostal space. Pain can also be referred to somatic structures without tumour infiltration of somatic nerves. [6] If infiltration to retroperitoneal nerves of the upper abdomen occurs, patients may present with debilitating pain. [97] Owing to nociceptive sensitive areas which are located within the liver capsule and biliary tract, right upper quadrant pain may be felt if liver metastasis occurs. Some patients with liver metastasis may also suffer from referred pain at the right shoulder or neck. [6,110] Patients with intestinal obstruction would experience colicky pain along with abdominal distention. [110]

Successful palliation of pain associated with pancreatic cancer starts with physical examination and comprehensive pain-directed history taking, including pain location, duration, temporal nature, exacerbating factors, alleviating factors, tried pain medication and related adverse effects of pain medication. [113] It is important to note that 80% of patient suffering from pain can be palliated using basic management. [110] Opioid analgesics are deemed to be the first-line medical management of pain from pancreatic cancer, and adequate pain palliation can often be achieved with opioid therapy alone. Treatment for intermittent and episodic pain is commonly started on an as-needed basis with short-acting opioids including oxycodone and morphine. [113] Patients can then be switched to around-the-clock opioid regimen if the pain becomes persistent, combined with a “rescue” dose for breakthrough

pain at about 15% of the 24-hour baseline dose. [6] Meanwhile, long-acting, sustained release opioid can be considered if the dosing schedule interferes with sleep in order to improve convenience and compliance. Patients who experience pain with neuropathic component can be benefited from the use of methadone due to its N-methyl-D-aspartate receptor antagonism properties but challenges such as unpredictable half-life and multiple drug-drug interactions suggest that it should only be considered as a first-line treatment option by clinicians experienced in its use. [113] The oral route is usually preferred for chronic pain management because of convenience and flexibility but pain control may also be achieved using transdermal route of administration, particularly in patients with persistent nausea and vomiting. Common dose-limiting side effects of opioids include sedation, nausea, respiratory depression and constipation, with quick development of tolerance towards the former three side effects. However, development of tolerance to constipation is unlikely and therefore it is of utmost importance that opioid analgesics are prescribed concurrently with a stool softener. [110,113]

Intervention techniques including celiac plexus neurolysis (CPN) and radiation therapy (RT) are useful as adjunctive treatment in patients whose pain is poorly controlled with opioids and thus require dose escalation and/or experience significant opioid associated adverse effects. [6,98,112-115] CPN is a technique of splanchnicectomy of the celiac plexus performed under local injection of absolute alcohol to ablate the afferent nerve fibers that are responsible for pain transmission from intraabdominal viscera including the pancreas on the basis that visceral afferent nerve fibers travel with sympathetic efferent nerve fibers. [112,113] CPN can be performed with any one of the three modalities which include surgical splanchnectomy, percutaneous (PQ)-CPN under fluoroscopy or computed tomography guidance, and endoscopic ultrasound guided (EUS)-CPN. [112] Multiple studies have demonstrated the success of CPN in pain management. A meta-analysis with twenty-four studies carried out by Eisenberg *et al*. reported that pain relief is achieved in 90% of the patients at 3 months after initiating CPN, with 70% to 90% of them having pain relief until death. [116] In a meta-analysis with 6 randomised controlled trials, patients receiving CPN had significant pain relief at 4 weeks compared to pharmacological therapy alone. [117] A meta-analysis of five randomised controlled trials comparing CPN to medical management reported a significant lower visual analogue scores and opioid usage in patients receiving CPN. [118] Another meta-analysis of nine randomised controlled trials performed by Puli *et al*. showed that more than 80% of patients having pain relief with (EUS)-CPN compared to non-interventional techniques. [119] A RCT carried out by Wyse *et al*. reported that patients randomised to (EUS)-CPN had greater pain relief compared to those who did not undergo the intervention. [120] Nevertheless, controversies exist regarding the most appropriate modality to be chosen as there are lack of well-designed randomized controlled trials and lack of studies directly comparing the available modalities. [112] (EUS)-CPN is the preferred modality but other minimally invasive modalities, such as fluoroscopic and CT-guided (PQ)-CPN, can be used when (EUS)-CPN is not available.[98] Predictors of successful outcome from CPN include lower doses of systemic opioids at the time of the procedure and absence of sedation when undergoing the procedure while predictors of unfavourable outcome from CPN include direct tumour invasion of the plexus and unilateral injection. [113,114] For patients who have recurrent pain attacks, they may undergo a repeat procedure although the success rate tends to be lower and mean duration of pain relief is decreased by more than half of that achieved in initial CPN particularly in patients whose radiographic imaging showed disease progression. [113] Complications and side effects described are usually mild, which include transient asymptomatic orthostatic hypotension particularly in elderly patients with comorbidity and diarrhea due to vasodilation and unopposed parasympathetic tone respectively. [110,113,114,121] Rare but significant complications include paraplegia, lower extremity weakness and paraesthesias possibly due to spasm or thrombosis of the artery of Adamkiewicz which supplies the inferior spinal cord, pneumothorax secondary to alcohol injection, as well as alcohol intoxication, seizure, incontinence, nerve damage, ischemic gangrene of the bowel and even paralysis. [6,113,114]

RT may be useful for palliation of pain due to local invasion of pancreatic tumour. [6] A study of high-dose (70-72 Gy) conformal RT for

patients with locally advanced pancreatic carcinoma over a period of 7-week in 44 patients reported pain relief in 68% of patients during or after treatment with a median pain-progression-free duration of 6 months. [122] Another study by Minsky *et al*. showed that improvement of pain symptoms was achieved within 8-12 hours in 104 patients treated with precision high-dose radiation therapy (50 Gy with a cone down to the tumor of 65 Gy). [123] However, CPN is usually preferred over RT when feasible since the pain relief is generally faster with CPN.

3.2.6 Intestinal obstruction

It was reported that approximately 10% to 20% of pancreatic cancer patients will develop duodenal obstruction as one of the complications which subsequently leads to gastroduodenal outlet obstruction. [90,124,125] Although gastroduodenal outlet obstruction is commonly present as preterminal event, it is most often not present at diagnosis. [6,90,126] The symptoms associated with duodenal obstruction include nausea, vomiting, weight loss, anorexia, cachexia, abdominal distension and inability to consume food or liquid. [124-127] Malnutrition often ensues to contribute significantly to the morbidities of patients and rapidly deteriorate their quality of life thereby causing the illness to progress to a terminal state. [124,126,127]

Creation of a prophylactic palliative gastrojejunostomy with a biliary bypass is a prevention strategy in those who are considered to be unresectable at exploration. [90] The benefit of this strategy was demonstrated in a meta-analysis of three prospective trials which compares prophylactic gastroenterostomy plus biliodigestive anastomosis with no bypass or a biliodigestive bypass alone. It was found that patients undergoing prophylactic gastroenterostomy had a significant lower risk of developing a gastric outlet obstruction during follow-up. The authors also reported an average duration of three days longer of hospital stay in those who underwent prophylactic gastroenterostomy. [128] Nevertheless, 26% of patients developed delayed gastric emptying (DGE) after a prophylactic gastrojejunostomy. [129]

Before defining treatment options, it is of utmost importance to assess the aetiology by performing history taking and physical examination. Many patients have advancing tumour with associated poor performance, immobility, dehydration, and taking opioids for pain control. As a result, the differential diagnosis must consider advancing of the cancer, decreased bowel motility, ileus, opioid-induced nausea and constipation. [6] CT scan with oral contrast or upper gastrointestinal series to assess the anatomy, length of the stricture, and degree of obstruction may be helpful, particularly in cases where it is unclear if the obstruction is functional. [130]

The goal of treatment includes achieving the remission of symptoms as complete and as prolonged as possible with intervention that is associated with least number of morbidity and mortality. [124,131] Treatment option that can achieve goal of treatment aforementioned adequately is still controversial and it depends on several factors such as the age of the patient, past treatments and closeness to death. Nasogastric suctioning and fluid replacement are helpful but often only for a short period of time. Pharmacological therapy that includes dexamethasone, haloperidol, and octreotide can be useful to some patients present with intestinal obstruction, nausea, and increased intestinal secretions. [6] Nevertheless, the more popular palliative treatment options for duodenal obstruction are surgery and endoscopy which are associated with initial success rate of more than 90%. [124]

Palliative surgery is mostly chosen over curative surgery since majority of the patients are not candidates for curative surgery due to poor surgical risks. [6,132] Palliative surgery with gastrojejunostomy (GJ) has been the traditional first-line treatment. [132,133] Conventional open GJ is associated with high pre- and postoperative morbidity and mortality rates due to inadequate regaining of per oral ingestion secondary to DGE and tumour bleeding. [126,128,132-135] DGE represents a serious problem for patients because it can cause deterioration of their quality of life. A regression analysis showed that preoperative obstruction was the most significant predictor of DGE and the incidence ranges from 7% to 26%. It was showed that DGE resulted from reflux of jejunum contents into the stomach through the stoma. [127]

To overcome the problems associated with conventional open GJ, the procedures have been modified and met with considerable success. Exclusional GJ originally devised by Devine has been used as palliative treatment for unresectable stomach cancer and resulted in prolonged life expectancy compared to

conventional open GJ but it was associated with epigastralgia in some of the patients after the procedure. [127] Kato *et al*. modified the original procedure of exclusional GJ but it was also associated with reflux problems similar to that described in conventional open GJ. This prompted Suzuki *et al*. to introduce adaptation of modified Devine exclusional GJ procedure devised by Kato *et al*. and performed laparoscopically in eight patients. All patients were found to regain adequate per oral ingestion. The adaptation was able to restore a satisfactory state of per oral ingestion as the reflux of the contents of afferent jejunum are prevented. [127] In addition, a laparoscopic stomach-partitioning GJ that also incorporates a modification of the Devine procedure is reported to be able to restore per oral ingestion in all patients with a median duration of 88 days besides improving the quality of their remaining life. [126] Overall, GJ that is performed laparoscopically is minimally invasive and is associated with lower morbidity and mortality rates as well as more favourable outcomes in terms of intraoperative blood loss, time to oral solid food intake, length of hospital stays and delayed gastric emptying compared to conventional open GJ. [124,126]

Endoscopic palliation involves insertion of a self-expanding metallic stents and is preferred over palliative gastrojejunostomy for patients with a symptomatic gastric outlet obstruction who are not attempting surgical resection. [124] The stent will expand to a size of 18 to 22 m and extend to a length of 6 to 12 cm once deployed. [131] Patients being considered for stent placement should have a life expectancy of less than two to six months. [136,137] The procedure is best performed in a room equipped with fluoroscopy by therapeutic endoscopists who are experienced with the placement techniques. [130] Technical and clinical success rates as reported in the literature are 92% to 100% and 77% to 100%, respectively. [125,131,138] A multicentre study reported that 84% of patients regain per oral ingestion after enteral stent insertion. [138]

The long term outcome of duodenal stent placement in palliative treatment of patients with unresectable adenocarcinoma of the head of pancreas is favourable in which the duodenal stent patency was able to remain for a median duration of 6 months as reported in a retrospective study conducted by Maire *et al*. [138] There was no improvement in stent patency in patients receiving chemotherapy for their unresectable pancreatic cancer. [137] Early intraprocedural adverse events include sedation, stent malposition, gastrointestinal haemorrhage, aspiration pneumonia, jaundice or cholangitis due to compression of the common bile duct, and rarely acute pancreatitis from compression of the pancreatic ductal orifice. [131,139] These complications occur in 2% to 12% of patients.[131] Late complications include distal stent migration, stent occlusion, bleeding, perforation, fistula formation, and occlusion of biliary stents. [139]

The main causes of failure include downstream obstruction by unrecognised peritoneal carcinomatosis which can lead to multilevel obstruction or gastroparesia possibly due to encasement of the vagal nerve or mesenteric vessels by the tumour, insufficient length to bridge the stenosis, stent obstruction due to food impaction, tumour ingrowth or tumour overgrowth, stent migration and functional gastric outlet obstruction from neural tumour involvement. [125,131,132] Tumour ingrowth and stent migration lead to recurrent duodenal obstruction in one quarter of the endoscopically palliated cases. [124] Stent obstruction is usually managed by a repeat procedure with placement of additional stents through the original stents. [131,140] Meanwhile, to reduce the risk of stent migration, duodenal stenting should be reserved for symptomatic patients as insertion of stent into non-critical structures has higher risk of stent migration. If there is concomitant jaundice, endoscopic palliation begins with the placement of a metal biliary stent before placement of the duodenal stent. If a biliary stent has previously been inserted, its patency should be confirmed before placing the duodenal stent with replacement if necessary. [131] Placement of a duodenal stent was a risk factor for biliary stent dysfunction in which 52% of patients presented with biliary stent dysfunction after duodenal stent placement. [141] However, it seems that combined biliary and duodenal stenting is a safe and effective palliative measure for inoperable malignant biliary and duodenal obstruction. [135,142] A success rate of 91% was reported in unresectable pancreatic carcinoma patients underwent combined biliary and duodenal stenting. [131] Long-term effective palliation was able to achieve with very few complications. [131]

Controversy exists about how to provide optimal palliative treatment since both surgical and endoscopic palliative procedures provide relief of duodenal obstruction. In a systematic review of 44 studies that compared enteral stenting to GJ, no significant differences were reported for technical success, early complications, late major complications and persisting symptoms. Initial clinical success rate and recurrent obstructive symptoms were higher with stent placement. Mean survival was found to be longer with GJ. [143] Gastrojejunostomy has also been reported to be superior in terms of long-term results. [144] In another study, no significant differences were found in terms of morbidity and mortality, but the median time to resume oral intake was 1 day for stent patients and 9 days for surgery patients. The authors also concluded that duodenal stenting was more beneficial than surgical gastrojejunostomy in enhancing patients' quality of life as improvement in the performance score was observed more frequently in patients underwent duodenal stenting. [145] In terms of length of hospital stay and cost, duodenal stenting was also found to be more favourable compared to surgery. [124,125,131,138] Nevertheless, Kubota *et al*. demonstrated that the stomach-partitioning GJ, which is a modified GJ procedure aforementioned, was better than endoscopic stenting in terms of quality of life and prognosis. [126] In addition, surgical palliative procedures are much more durable and require less re-intervention compared to endoscopic stenting. [124] The decision to perform either surgical or endoscopic palliation in pancreatic cancer patients present with duodenal obstruction may be depending on life expectancies of the patients, in which stent placement is the treatment of choice for patients expected to live less than 2 months while GJ is the treatment of choice for patients expected to live more than 2 months because the initial success rate was higher with patients underwent duodenal stenting. [136]

3.2.7 Delayed gastric emptying (DGE)

According to a study of fifteen patients with pancreatic cancer, up to 60 percent of them have slowed gastric emptying although there is no evidence of gastroduodenal tumour invasion tumour. [146] The pathogenesis of DGE has been postulated, which include infiltration of tumour into the retroperitoneal nerve plexuses, autovagotomy due to micrometastasis, production and secretion of tumour-related gastroparetic factor or inhibitory neurotransmitters, such as vasopressin, by the tumour, disruption of the neuroendocrine feedback inhibitory cycle and paraneoplastic involvement with antineuronal antibodies. [146,147] Approximately one-third of pancreatic cancer patients with delayed gastric emptying present with nausea and vomiting, which may be mistakenly thought to be secondary to gastric or duodenal obstruction. Vomiting may be managed with a prokinetic agent such as metoclopramide although the successful management of vomiting is difficult. [146] For refractory cases, several non-pharmacologic interventions are available for decompression, such as employing "draining" percutaneous endoscopic gastrostomy tube (PEG) or a nasogastric tube. [147]

3.2.8 Depression

It has been known for several decades that depression is more prevalent in pancreatic cancer patients than those with other types of malignancies. Fras *et al*. conducted a study in 139 patients who were admitted for possible pancreatic or colon cancer and reported that 76% of patients with pancreatic cancer had depressive symptoms prior to surgery while only 20% of colon cancer patients suffer from depression. [148] Joffe *et al*. showed that half of the patients who were eventually diagnosed with pancreatic cancer met the criteria for the diagnosis of depression while no patients that were eventually diagnosed with gastric cancer met the criteria. [149] In a comprehensive review conducted by Massie *et al*., the prevalence of depression in pancreatic cancer was found to be 33% to 50%. [150] Pain, which is also commonly described in pancreatic cancer patients, is found to have some association with depression in which depressed pancreatic cancer patients were reported to have more intense pain compared to those who are not depressed besides experienced a significant impairment of their quality of life. [151] These features can be improved if depression is properly managed. [152] Depressive symptoms may also subside in patients with pancreatic cancer if the tumours have been surgically excised. [6]

There are studies which proposed that depression may be linked to paraneoplastic limbic encephalitis and it was found that depression precedes pancreatic cancer symptoms just as the paraneoplastic limbic encephalitis often precede cancer diagnosis. [153,154] Meanwhile, another school of thought

proposed that a dysregulated immune response may be associated to both depression and cancer since it was shown that proinflammatory cytokines can produce "depression-like" symptoms in animal models. In fact, levels of several cytokines such as interleukin-6, interleukin-18 and TNF-α are found to be elevated in pancreatic cancer patients. [154] Increased interleukin-6 plasma levels in particular was found to be correlated with a diagnosis of major depression in pancreatic cancer patients in one study. [155] In addition, pancreatic tumours were found to be associated with increased serotonin secretion which caused alteration in its metabolism thereby decreasing the serotonin in the central nervous system and subsequently caused depression in pancreatic cancer patients. [156]

Pharmacological therapy with antidepressants are the mainstay of management for cancer patients present with moderate to severe depression since they were found to be able to alleviate depressive affect, emotional lability, irritability, and social withdrawal. [157] Treatment usually consists of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) or a combination of both. [103,156] Interestingly, lower doses of TCAs were required to exhibit a therapeutic response in cancer patients compared to physically healthy individuals. [158] SSRIs as a class are the most widely used antidepressants and the efficacy of SSRIs in pancreatic cancer patients may be explained by the altered metabolism of serotonin aforementioned. [156] They generally have less sedative, autonomic and anticholinergic side effects as compared to TCAs therefore causing fewer problems with cardiac arrhythmias, hypotension, dry mouth and somnolence. [103] However, the analgesic properties of TCAs may benefit patients who are suffering from cancer-related pain, especially those with neuropathic component. [103,156] Combined therapy with TCAs and SSRIs are particularly advantageous for cancer patients present with depression and anxiety or insomnia.

Brief psychosocial intervention (ie, psychotherapy of fewer than six sessions with a psychiatrist) and cognitive therapy appear to be beneficial for patients in a palliative setting through addressing of patients' depressive symptoms. [6]

3.2.9 Fatigue

Fatigue is one of the most commonly encountered symptom in cancer patients which can negatively affect quality of life and emotion as well as social relationships. [6,103] It is important to note that patients' ability to retain information and to continue with their treatment regimen may be influenced owing to profound cancer-related fatigue, which could possibly affect the success of cancer treatment. [6] There are several possible factors which can potentially contribute to fatigue in patients with pancreatic cancer, including depression, pain, opioid use, anaemia, chemotherapy with or without radiation and its side effects, insomnia, dehydration, and cachexia. In addition, the abnormal production and distribution of cytokines are also associated with fatigue. Treatment is often focused on obvious correctable factors including pain, anaemia, insomnia, depression, and dehydration. [6] Anaemic cancer patients can be managed with recombinant human erythropoietin to maintain an adequate haemoglobin level. [103]

The effect of methylphenidate with psychostimulating properties has been evaluated by Escalante *et al*. in 33 breast cancer patients. 64% of patients reported subjective improvement in their cancer-related fatigue and more than half of the patients wanted to continue with the treatment due to excellent tolerability of the drug. [159] Therefore, it is suggested that methylphenidate can be useful for pancreatic cancer patients who experience cancer-related fatigue. [160] Vitamin D and its analogue are another investigational therapy for cancer-related fatigue. In a prospective study conducted by Trivanovic *et al*., statistically significant improvement in fatigue as measured by Functional Assessment of Cancer Therapy Fatigue scale was reported in patients receiving 2,000 IU of Vitamin D3 daily for 3 months. [161] Since vitamin D is cheap, easily available and almost tolerable by every patient, it can be offered to pancreatic cancer patients with fatigue and low vitamin D levels. [103]

3.3 Other approaches to palliative care

3.3.1 Physical Therapy

Physical therapy plays a significant role in reducing premature death of cancer patients caused by physical inactivity. To achieve pain relieving effect, the modalities of physical therapy can range from using heat, cold, and transcutaneous electrical nerve stimulation. The

goal of physiotherapy is to help the patients maintaining optimum respiratory and circulatory function, which in turn could prevent muscle atrophy. [162] It can also indirectly optimise independence of cancer patients and promote interaction between cancer patients and their families.

3.3.2 Complementary Medications

Today, the popularity of the usage of complementary indigenous Malay therapies (CIMT) within palliative care in Malaysia is undeniable because it is rather easy and simple to be used. Moreover, they believed that complementary medications are able to enhance overall well-being of the terminally-ill. Among the available complementary medications, the most preferable types of CIMT are dried medicinal roots, herbs and sea cucumber products. However, most of the CIMT users claimed that they generally exhibit significantly poorer physical symptoms than the non-CIMT users. [163]

3.3.3 Nutrition

For terminally ill patients, cancer treatment can exert a huge impact on their appetite. In the worst case, their ability to eat and drink would be affected. Hence, nutritional care should aim to reduce the discomfort associated with food intake by tailoring to patient's needs. Sometime, enteral or parenteral nutritional support is also required to assist in the food feeding. [164]

3.3.4 Massage Therapy

Pain, anxiety, and depression usually occurs in the care and treatment of terminally ill patients as the disease continues to progress. Although opioid analgesics are usually given to alleviate pain, side effects such as respiratory depression, constipation and dependency can be noted. At this moment, patients frequently turn to massage therapies. Massage therapy has a proven effect in reducing subjectively perceived symptom of pain in palliative care patients. Apart from that, remission of the symptoms of anxiety and depression can also be achieved. [165]

3.4 Measuring the efficacy of palliative care

There is no gold standard quality of life measurement to assess the efficacy of palliative interventions. [166] Various tools such as EORTC and The Functional Assessment of Cancer Treatment (FACT) have been developed to permit the systematic, reproducible assessment of patients' quality of life. [167] However, the implementation of these tools by the oncology researcher in clinical practice has been difficult as it is generally applicable toward all cancer or it may be too detailed for the patient. [168] Nevertheless, communication with patients is practised to determine the efficacy of palliative treatment regimen. [169]

3.5 Challenge associated with palliative care

One of the issues associated with palliative care is the late timing of palliative care referral, which is a significant barrier for optimum patient care. Referral to palliative care depends on the individual clinician and is heterogeneous. [170] The curative potential of anticancer therapies, the need to respect patients and family adaptation process, coping mechanisms and the fears regarding end-of-life conversations are some of the concerns of clinicians that early referral to palliative care could have negative effects on patients' and their family members' hope. [76,78] Late referral is an obstruction for appropriate stabilisation of patients' emotional and physical distress and advance care planning. This could cause the effective discharge to the community to become more complex. Prognostication inaccuracy could be also one of the valid reasons for the late referral to palliative care since prognosis is applied on populations but it may vary individually. [170]

Many physicians fail to appreciate the impact of symptoms on the patient's quality of life or may lack an understanding of how to treat the whole patient rather than just the tumour. These problems can be attributed to a lack of knowledge and skills in palliative care since there are still many aspects such as holistic approach, symptom management and communication skills that is yet to be integrated as a part of the medical, oncologist and radiotherapist training. For instance, pain control is rather late to be included in the Medical Oncology Board examinations although pain is a dominant cancer symptom. [166] Therefore, palliative care should be included in medical curricula and medical training for students and post-graduates. There is also a need to integrate palliative care into the existing system since it is still seen as an uncommon and luxurious care for a small group of patients after completing their anticancer therapy. Palliative care should be provided in hospitals and cancer centres and research should be integrated into palliative care to validate the symptom and pain management and to show the improvements in quality of life as well as to prove its cost-effectiveness. [77]

Moreover, due to the aging of the population, oncologists will be increasingly faced with managing cancer patients who have a variety of other concomitant age-associated illnesses, including osteoarthritis, diabetes and congestive heart failure. Therefore, oncologists will require training in the appropriate use of palliative treatment regimens as well as in the treatment of patients with advanced cancer who have multiple diseases and associated symptoms. [166] Oncologists also face a challenge to determine whether further palliative treatment remains valid as disease progresses. [6] There is no benefit to continue anticancer treatment that fails to prolong life, improve functional limitation or reduce symptoms of illness. At this point, management measures should focus on pain and symptom distress. The medical oncologist should know not only when interventions are indicated, but also when they are not. [171]

Measuring palliative care outcomes are equally important to the interdisciplinary team in management of patients with advance cancer. However, three important challenges exist in measuring the outcomes of palliative care: whose perspective should be captured, who is the person measuring the outcomes, and the availability of appropriate tools which are valid and reliable to capture meaningful data. Data sources include patients, proxies (i.e., family caregivers), clinicians, and administrative data bases. [172] Each has benefits and drawbacks to consider that should relate specifically to the question to be answered. It is also costly in terms of staff time or identifying non-staff interviewers, chart auditors and other data collectors when measuring the outcomes. In addition, clinically meaningful tools used in gathering data from seriously ill patients are only beginning to be developed although there are many developed tools used in research. [172]

3.6 Future directions of palliative care

To establish a sustainable palliative care system in future, introduction of palliative care into undergraduate education is strongly recommended as it can effectively broaden the coverage of palliative care at national level. In addition, regular training should be conducted to allied health professionals or social workers so that doorstep palliative care can be carried out in the near future. [173]

Current health care system stresses on referring patients to palliative care when there is no available treatment to improve their conditions. Therefore, patients also tend to reject palliative care treatment as they believe that it is a preparation to death. However, it is crucial that early introduction of palliative care to patients and their families should be integrated in current health care system. This enable them to familiarise with the services provided by palliative care and it is easier for the palliative care team to communicate with the families about death at the beginning. [174] This can particularly change the mindset of patients in receiving palliative care treatment.

To deliver a high-quality palliative care, it is essential to conduct research and clinical trials to optimise the interventions provided currently. It is a fact that discoveries such as megestrol for treating cancer cachexia, biphosphonates for pain management in bone metastasis and opioids for the palliation of breathlessness in terminally ill patients were resulted from the research in palliative care. [174] Therefore, research and development in palliative care should be emphasised.

4. Predicting survival and prognosis

Even in the setting of completely resected, node-negative pancreatic cancer, the majority of patients die of their disease. The most important prognostic factor for completely resected patients is nodal status in which five-year survival after pancreaticoduodenectomy is 7.8% for node-positive disease, while it is 41.7% for node-negative disease. [175]

Tumour stage is also an important prognostic factor. The influence of tumour stage on survival can be illustrated by a series of 21,512 patients undergoing pancreatectomy for pancreatic adenocarcinoma and reported to the National Cancer Database between 1992 and 1998. [176] The reported stage predicted 5-year survival are of the followings: stage IA, 31.4%; IB, 27.2%; IIA, 15.7%; IIB, 7.7%; III, 6.8%; IV, 2.8%. [171]

In addition to cancer stage, other factors that influence prognosis after resection are the status of the surgical margins (involved or uninvolved), possibly the width of the surgical margin, tumour size, tumour differentiation and the presence or absence of lymphatic invasion within the tumour, and both preoperative and postoperative serum CA 19-9 levels. [177-180]

Finally, the number of negative nodes examined also impacts prognosis. Data supported the view that pathologic examination of at least 15 nodes in the pancreatectomy specimen is necessary to accurately stage a node-negative

adenocarcinoma. A median survival difference of 8 months in favour of the patients who had 15 or more examined nodes compared with patients with fewer than 15 examined nodes was reported. [181]

A postresection nomogram has been developed and validated to predict the probability that a patient will die of pancreatic cancer within three years of surgery. [182,183] In addition to the tumour (T) and nodal (N) status, this nomogram incorporates clinical (age, sex, presence of back pain or weight loss, tumour location), pathologic (histologic differentiation, tumour size, margin status, number of positive nodes), and surgical (type of resection) variables. [183]

CONCLUSION

Pancreatic cancer is a complex malignant disease with high lethality. Despite extensive research, the survival rates in pancreatic cancer still remains dismal. Surgery is the only curative option. Adjuvant therapies with chemotherapy and radiation, though improves the disease to some extent, are not yet optimal. Recent reports note activity with immunotherapies. Some of which are already being exploited in clinical trials and have proven to be a promising treatment for pancreatic cancer. Palliative care represents an important aspect of care in patient with pancreatic malignancy. When initiated early in the disease course, palliative care has been shown to improve clinical, quality of care, and survival outcomes. Early formal consultation with palliative care is therefore strongly urged in patients with advanced pancreatic cancer. Identifying and treating disease related symptomology are priorities of palliative care. It is important for oncologists to recognise the supportive measures which aim to palliate the symptoms of advanced cancer and integrate them into routine care of pancreatic cancer.

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