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Pancreatic Neuroendocrine Tumors: Emerging Management Paradigm

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1. Introduction

Neuroendocrine tumors comprise a spectrum of slow growing neoplasm, characterized by storage and secretion of variable peptides and neuroamines (Massironi et al., 2008). Pancreatic neuroendocrine tumors (PNET) are relatively rare, with an estimated incidence of less than 1 per 1000,000 individuals (Metz and Jensen, 2008). A recent review of surveillance epidemiology and end results (SEER) (1950-2007) database reported the frequency of PNET to be around 7% among all identified neuroendocrine tumors (Lawrence et al., 2011a). Furthermore, they comprise 1-2% of all pancreatic neoplasms (Metz and Jensen, 2008). However, the incidence is considered to be increasing , perhaps in part due to improved diagnostic capabilities. Median overall survival in PNET ranges from more than 10 years in localized disease to approximately 2 years in metastatic disease (Yao et al., 2008a). Recently, considerable headway has been made in the realm of therapeutics. Therefore, it is imperative that oncologists today have a heightened awareness of this disease entity in order to provide effective care.

2. Diagnosis, staging and classification

PNETs have also been referred to as pancreatic endocrine or islet cell tumors. It is important to note that carcinoid and PNETs, although exhibiting identical characteristics histologically, should be considered separately. It is increasingly clear that these two tumor types are different in their biology and response to therapy. The clinical presentation of PNET is extremely variable which depends on the originating cell type and whether there is secretion of active hormones. Majority of patients remain asymptomatic, but a significant proportion present with clinical symptoms and hepatic metastases at the time of diagnosis (Modlin et al., 2008).

Most cases of PNET occur sporadically, however, approximately 10% of cases may be associated with multiple endocrine neoplasia type 1 (MEN1). MEN1 is an autosomal dominant syndrome associated with mutations in the tumor suppressor gene *menin* and characterized by multiple neuroendocrine tumors in the pancreas, parathyroid and pituitary glands (Agarwal et al., 2004). PNETs have also been associated with MEN2, Von Hippel-Lindau disease, Tuberous sclerosis and Neurofibromatosis (Kulke et al., 2011). Although the incidence of these inherited syndromes is low, it may be important to consider these syndromes in the diagnostic work up of patients with PNETs.

It is important to discern the diagnosis of PNET from the more common pancreatic adenocarcinoma. Grossly, PNETs are solitary well demarcated, tan soft tumors which can have a nodular appearance, when they exhibit fibrosis. The histological criteria for diagnosis are well established. These tumors can range from well differentiated ,low grade tumors to more poorly differentiated high grade types. Well differentiated tumors can exhibit various histological patterns, ranging from a common solid nesting, trabecular to tubular-acinar and mixed patterns .The cells are characterized by round to ovoid shape, with eosinophilic granular cytoplasm and prominent nucleoli. Unusual types can exhibit a spindle cell morphology which is referred to as the "rhabdoid" type. High grade malignancies with high mitotic rate usually encompass large cell and small cell carcinomas (Asa, 2011).

The usually employed classification schemes, although inconsistent in their criteria, reflect a basic separation between more indolent, well differentiated and aggressive poorly differentiated ones. While a number of histologic classification systems have been proposed for PNET, tumors with high mitotic count (>20/10 high power field) or a Ki-67 proliferation rate of >20%, generally represent highly aggressive malignancies and should be evaluated apart from the more classic well differentiated tumors such as classic carcinoid or islet cell type. These high grade malignancies are generally treated according to small cell carcinoma guidelines (Asa, 2011; Kloppel et al., 2004; Rindi and Kloppel, 2004). Table 1 outlines the histologic classification of neuroendocrine tumors.

Differentiation	Mitotic count	Grade	Ki-67 index (%)	General features	ENETS, WHO classification
Well differentiated	<2 per 10 HPF	Low Grade (G1)	≤2	Without local invasion (angioinvasion or perineural invasion). Traditionally include carcinoid and PNETs	Neuroendocrine tumor grade 1, WHO type 1.1 (pancreatic)
	2-20 per 10 HPF	Intermediate grade (G2)	3-20	With or without gross local invasion or metastases. Traditionally include carcinoid, atypical carcinoid and some PNET	Neuroendocrine tumor, Grade 2, WHO type 1.2 and 2 (pancreatic)
Poorly Differentiated	>20 per 10 HPF	High Grade (G3)	>20 %	Small cell or large cell carcinoma, often widely invasive or metastatic.	Neuroendocrine Carcinoma grade 3 (small cell or large cell), WHO type 3 (pancreatic)

ENETS: European Neuroendocrine Tumor Society; WHO: World Health Organization.

Table 1. Histologic classification of Neuroendocrine Tumors.

Several organizations, including the European Neuroendocrine Tumor Society (ENETS), and the American Joint Committee on Cancer (AJCC), have proposed staging systems for neuroendocrine tumors using the TNM notation (Edge and Compton, 2010). Although these two staging systems are similar for tumor arising in the luminal gut, they differ for earlier stage PNETs. The ENETS system incorporates tumor diameter in its assessment for T stage, whereas the AJCC incorporates factors determining resectability. However, both systems are nearly identical in defining stage IV disease. Because the AJCC system has been widely accepted and adopted in North America, this is preferably and more commonly used for classification by tumor stage.

3. Clinical manifestation

When functional, PNETs can be characterized by the type of hormone secreted leading to a specific clinical manifestation (Table 2). Specific details about some common tumors, based on the presentation are discussed below.

3.1 Insulinoma

Insulinomas are the most common PNET, comprising 30-40% of these tumors. Overall, they remain a rare entity with an incidence of approximately 0.4/100,000 patient years (Mathur et al., 2009).Classically, they present with "Whipple's Triad": a combination of symptoms of hypoglycemia, inappropriately high insulin level and associated blood glucose levels of <50 mg/dl with relief of symptoms on administration of glucose (Whipple and Frantz, 1935). In a 25-year Massachusetts General Hospital experience with insulinoma, the most common clinical symptoms in this series of 61 patients were confusion, visual disturbances and diaphoresis (Nikfarjam et al., 2008). Biochemical diagnosis requires confirmation of inappropriately elevated insulin, C-peptide and proinsulin levels in the presence of low serum glucose. Biochemical diagnosis is usually followed by radiological (CT or MRI) or endoscopic diagnosis. At early stages, the hypoglycemia can be managed with diazoxide and somatostatin analogues should be used cautiously as it can worsen hypoglycemia (Goode et al., 1986). Everolimus, an mTOR inhibitor, has been reported to be efficacious in cases of refractory hypoglycemia (Kulke et al., 2009a).

3.2 Gastrinoma

Gastrinoma and Zollinger-Ellison syndrome are suspected in a patient with recurrent or refractory peptic ulcer disease and unexplained secretory diarrhea. In such patients, fasting gastrin level >100 pg/ml is highly suspicious of this diagnosis (Jensen, 1996). Other common causes of gastric hypersecretion should be excluded, which includes treatment with proton pump inhibitors (PPI), atrophic gastritis and pernicious anemia. Approximately 25% of patients will present with diarrhea as primary manifestation without peptic ulcer disease (Perry and Vinik, 1995). Gastrinomas have a strong predilection for a "gastrinoma triangle" that includes the pancreatic head, first two-thirds of the duodenum and the porta hepatis (Howard et al., 1990). A significant proportion of gastrinomas are malignant, with up to one-third of patients presenting with liver metastases (Mittendorf et al., 2006). PPI therapy is highly effective for initial symptom management and somatostatin analogues have also shown effectiveness in controlling symptoms and concomitantly offering tumor stabilization (Lambers et al., 1984; Shojamanesh et al., 2002).

3.3 Glucagonoma

Majority of the patients with glucagonomas present with a dermatitis called necrolytic migratory erythema, causing pruritis and often becoming secondarily infected (Perry and Vinik, 1995). The clinical manifestation may also include diabetes, depression and deep vein thrombosis. Glucagonomas are frequently found in the pancreatic tail and have a malignant potential with a predilection for metastases. A serum glucagon level >500 pg/ml is highly suspicious of the diagnosis, whereas, a concentration of >10,000 pg/ml is virtually diagnostic (Chastain, 2001). However, a normal level does not exclude the diagnosis as secretion of glucagon may be episodic and a high concentration may be seen in other clinical syndromes such as sepsis, renal and hepatic failure. Initial management with somatostatin analogues are usually very effective in controlling symptoms however, such treatment may not have an effect on tumor growth. (Jockenhovel et al., 1994)

3.4 Somatostatinoma

Pancreatic somatostatinoma are usually malignant, and can present clinically with a syndrome of diabetes, steatorrhea and cholelithiasis (Warner, 2005). The diagnosis can be confirmed biochemically with marked elevation of serum somatostatin followed by imaging and endoscopic ultrasound, as with other pancreatic neuroendocrine tumors. Management with somatostatin analogues may be effective in symptomatic patients.

3.5 VIPoma

Verner and Morrison first described pancreatic endocrine tumors with a clinical syndrome of watery diarrhea, hypokalemia and achlorohydria (Verner and Morrison, 1958). This syndrome was subsequently found to be due to ectopic vasoactive intestinal peptide (VIP) secretion. Biochemical analysis assists in establishing a diagnosis when a marked elevation (>200 pg/dl) in the serum level of VIP is found (Smith et al., 1998). Symptomatic control of the diarrhea can be achieved with somatostatin analogues (Kraenzlin et al., 1985).

Tumor Type	Symptoms or signs	Incidence of metastases
Insulinoma	Hypoglycemia leading to confusion, visual disturbance, diaphoresis.	<15% (Vinik and Gonzales, 2011)
Gastrinoma (Zollinger-Ellison Syndrome)	Abdominal pain, diarrhea (secretory), recurrent peptic ulcer disease	50-85% (Batcher et al., 2011; Mittendorf et al., 2006)
Glucagonoma	Diabetes, necrotizing migratory erythema, cachexia, depression, deep vein thrombosis	75% (Batcher et al., 2011)
VIPoma, Verner-Morrison syndrome,WDHA syndrome	Watery diarrhea (secretory), hypokalemia	70-80% (Vinik and Gonzales, 2011)
Somatostatinoma	Cholelithiasis, steatorrhea, diabetes	80% (Vinik and Gonzales, 2011)
Non-functioning	Abdominal pain, weight loss, jaundice	60-85% (Vinik and Gonzales, 2011)

WDHA: Watery diarrhea, hypokalemia and achlorohydria

Table 2. Clinical manifestation of Pancreatic Neuroendocrine Tumors.

4. Biochemical testing in PNET

As majority of PNETs are non-functional, hormonal assays cannot be used for clinical assessment. Hence, serum chromogranin A (CgA) has come to represent a common denominator peptide with the putative ability to serve as a marker of disease activity, in both functional and non functional tumors. Granins are found as major components of the soluble core of dense secretory granules in neuroendocrine cells and are secreted in a physiologically regulated manner (Kim et al., 2001). Eight members have been identified including CgA, chromogranin B, chromogranin C, SgIII, SgIV, SgV, SgVI and VGF nerve growth factor-inducible. Granins have been proposed as playing important roles in secretory granule formation and development. CgA was the initial member identified, and originally detected in the chromaffin granules of the adrenal medulla (Blaschko et al., 1967). Although the definitive function of CgA remains unclear, CgA derived peptides mediate a number of biologic functions including regulation of parathyroid hormone secretion, carbohydrate metabolism, lipid metabolism and catecholamine secretion etc (Lawrence et al., 2011b).

Serum concentrations of CgA may decrease in patients responding to somatostatin analogs or other therapies. CgA should be used with caution as a marker of disease activity in patients treated with somatostatin analogs, because these agents significantly reduce plasma CgA levels which may falsely reflect any change in tumor size. Increased CgA concentrations assist in the clinical evaluation of PNETs but they are not specific for this kind of malignancy. Benign causes of CgA elevation should also be taken into consideration which include renal insufficiency, liver diseases and in patient taking proton pump inhibitors. Therefore, use of CgA as a diagnostic or screening test for PNET is discouraged.

5. Conventional imaging and Somatostatin Receptor Scintigraphy (SRS)

Although conventional imaging which include CT or MRI scans are usually employed in the initial diagnostic workup, they detect less than 50% of most PNETs that are less than 1 cm, therefore frequently missing small tumors (especially insulinomas, duodenal gastrinomas) and small liver metastases (Noone et al., 2005; Rockall and Reznek, 2007). Although, CT imaging with contrast is perhaps the most common initial imaging obtained, in certain clinical scenarios endoscopic ultrasound (EUS) paired with fine needle aspiration, remains the main endoscopic diagnostic technique. Several small studies reveal impressive diagnostic capability of this modality with reported sensitivity between 80% and 90% (De Angelis et al., 2011). EUS is much more effective for localizing intrapancreatic PNETs than extrapancreatic PNETs such as duodenal gastrinomas or somatostatinomas. Moreover, EUS is particularly helpful in localizing insulinomas, which are small, almost always intrapancreatic, and frequently missed by conventional imaging (Kulke et al., 2010a).

PNETs frequently overexpress somatostatin receptors and bind synthetic somatostatin analogues with high affinity. A number of radiolabeled analogues have been developed, with the most widely used worldwide and the only one available in the United States being ^{111}In-DTPA-octreotide (Octreoscan). SRS usually utilizes both planar imaging with either whole body scanning or multiple static acquisitions and single-photon computed tomography (SPECT). The latter modality can potentially improve the accuracy of SRS. This can allow SRS to detect up to 50% to 70% of primary PNETs and more than 90% of patients with metastatic disease. False-positive localizations can occur in up to 12% of patients, so it is important to interpret the results cautiously (Dabizzi et al., 2010; Kulke et al., 2010a) .

6. Role of surgery and liver directed therapy

The therapeutic plan of PNETs is based on the histologic classification and tumor stage. Surgery remains the cornerstone of treatment of early stage PNETs. Surgical resection of localized PNETs offers excellent prognosis and curative potential. Depending on the site and size, in the absence of distant metastases enucleation may be sufficient. This approach can easily be employed for many PNETs specially insulinomas, small non functioning PNETs (<2 cm) and small gastrinomas (Kulke et al., 2010a) . The long term survival in certain cases may exceed 90% (Service et al., 1991). Whipple pancreatoduodenectomy, left pancreatectomy or total pancreatectomy can offer a 5-year survival rates of 61%-79% even in some advanced cases (Dabizzi et al., 2010). The role of surgery in patients with MEN1 syndrome is complicated and remains controversial because the risk of additional neoplasms within the remaining pancreas and other sites (Demeure et al., 1991).

In patients with limited hepatic metastases, surgical hepatic resection may be feasible to debulk the tumor burden and help alleviate symptoms. Surgical resection of majority of the tumor is possible in only 5-15% of PNETs with hepatic metastases (Norton, 2005; Que et al., 2006). This approach can offer improvement in symptoms in over 90% of patients (Sarmiento and Que, 2003).Even though most of the evidence in this area is derived from uncontrolled studies, many agree that surgical resection should be attempted in malignant PNET with limited hepatic metastases if it is deemed possible that >90% of viable tumor can be removed (Kulke et al., 2010a).

In patients who are not candidates for surgical hepatic resection, hepatic arterial embolization remains a viable palliative approach. Important characteristics that are important for patient consideration is a preserved performance status , liver confined disease and a patent portal vein. Response rates are generally encouraging (>50%) as measured by either radiographic regression or hormonal secretion (Gupta et al., 2003; O'Toole and Ruszniewski, 2005; Toumpanakis et al., 2007). Although a number of techniques exist, including bland embolization, chemo-embolization or radioisotope-embolization, no data exist determining the superiority of one approach over another.

Other radiological approaches that can be employed in treating the hepatic metastases in malignant PNET, are radiofrequency ablation and cryoablation (Toumpanakis et al., 2007). These approaches may not be a feasible option in bulky hepatic disease and the benefit derived in small volume disease is also not clear. The advantage may be that these techniques seem to cause less morbidity. Therefore, careful patient selection is crucial to consider ablative techniques in order to avoid any unwarranted adverse effects.

7. Peptide Reception Radiation Technique (PRRT)

Majority of PNETs express somatostatin receptors, which provides a rationale for PRRT in selected cases. The most frequently used radionucleotides for PRRT are yttrium (^{90}Y) and lutetium (^{177}Lu), which have different physical and biological characteristics. One study reported encouraging results with 129 patients with malignant NETs treated with [^{177}Lu-DOTA-Tyr3]octreotate and resulted in a complete response in 2%, partial in 32%, and stabilization in 34% (Kwekkeboom et al., 2008). This form of treatment is generating widespread interest and more randomized studies are warranted in order to better explain its efficacy, role and toxicity.

8. Role of somatostatin analogs

The high expression of somatostatin receptors in PNETs also provides a rationale for utilizing somatostatin analogs for therapeutic purposes. In the PROMID study, which was a randomized, placebo-controlled, prospective trial in patients with midgut carcinoid, treatment with somatostatin analog octreotide was associated with improved time to progression over placebo (Rinke et al., 2009). Whether this hold true for PNETs, remains to be seen and is currently being explored in a number of ongoing studies. According to the National Comprehensive Cancer Network guidelines, somatostatin analogs should be considered in patients with hormone hypersecretion, although the authors do state that no randomized studies to date have demonstrated anti-tumor effect of somatostatin analogs in PNETs (Kulke, 2011). Octreotide 150-250 mcg subcutaneously three times a day or octreotide LAR 20-30 mg intramuscularly every 4 weeks can be considered for symptom control. Short acting octreotide can be added to octreotide LAR for treatment of breakthrough symptoms.

9. Cytotoxic chemotherapy

A number of chemotherapeutic agents have been tested in advanced metastatic PNETs, with encouraging results showing antitumor activity. Streptozocin was approved by the FDA in July, 1982 as a treatment for advanced PNET after initial studies showed sufficient antitumor effect and response rates. A number of studies by Moertel et al in the 1970's were crucial in this area. One trial randomized 84 patients to either streptozocin alone or streptozocin and fluorouracil. Based on non-standard criteria, 63% of patients were reported to have a response to therapy, with 33% complete responses in the combination arm (Moertel et al., 1980). Other combinations that have been evaluated are streptozocin/doxorubicin or streptozocin/doxorubicin/fluorouracil (Kulke et al., 2010a; Moertel et al., 1992). Treatment with streptozocin and doxorubicin was associated in a combined radiological and biochemical response rate of 69% with a median survival approaching 2 years (Moertel et al., 1992). Based on retrospective data, the 3-drug regimen of streptozocin, 5-fluorouracil, and doxorubicin is associated with an overall response rate of 39% and a median survival duration of 37 months (Kouvaraki et al., 2004) .The combination of 5-fluorouracil, Cisplatin and streptozocin was tested in a series of 82 patients with advanced neuroendocrine tumor, prospectively identified from a database .Sixty percent of patients in this series were identified to have a pancreatic primary. Although, limited by a number of weaknesses in the study, the investigators reported a response rate of 38% in PNETs (Turner et al., 2010). Patients with advanced poorly differentiated PNETs should be treated along the small cell carcinoma guidelines with therapy based on platinum regimens. This approach has been shown to result in a response rate of 40 to 70% (Kulke et al., 2010a). Although, these data support the antitumor activity of streptozocin based regimens, the acceptability of this approach has been limited because of a cumbersome administration schedule and toxicity profile.

Temozolomide has been combined with other biological agents such as thalidomide, bevacizumab and everolimus is phase II studies, yielding a response rate from 24-45% (Kulke et al., 2010b; Kulke et al., 2006a; Kulke et al., 2006b). Moreover, the combination of temozolomide and capecitabine has been reported to have an objective response rate of 70% (Strosberg et al., 2011) .There is also evidence to suggest that 0^6-methylguanine DNA

methyltransferase (MGMT) deficiency can predict treatment responses to temozolomide in PNETs (Kulke et al., 2009b). Considering the available data, temozolomide based treatment has comparable efficacy to streptozocin based therapies with favorable toxicity profile. Further larger trials are warranted to further elaborate the role of temozolomide in the context of modern treatment paradigm in PNET.

10. Biologically targeted therapies

Recently, a number of studies have demonstrated activity in PNETs, targeting the vascular endothelial growth factor (VEGF) signaling and the mammalian target of rapamycin (mTOR) pathways. Although, obejective responses have been persistently low across studies, improvements in progression free survival have been encouraging.

10.1 Targeting VEGF pathway

PNETs are characterized by upregulation of VEGF and VEGF receptor (VEGFR). This correlates with increased angiogenesis, metastases and can potentially lead to decreased progression free survival (Zhang et al., 2007). Tyrosine kinase inhibitors with activity against VEGFR, such as pazopanib, sorafenib and sunitinib, have been evaluated in advanced PNET demonstrating encouraging results. Pazopanib was evaluated in a multi-instituion phase II study treating a total of 51 patients , 29 of which had PNET. Patients received pazopanib 800 mg daily, in addition to octerotide LAR. The response rate among patients with PNETs was reported to be 17%. Median PFS was reported to be 11.7 months. Grade 3/4 toxicities were relatively rare and included anemia, neutropenia, hypertriglyceridemia and liver function derangement (Phan et al., 2010). Another phase II trial is evaluating the role of pazopanib in patients with neuroendocrine tumors who may have had treatment with antiangiogenic and mTOR inhibitors. The trial is currently accruing and is expected to complete accrual in September 2011 (Capdevila et al., 2011). Sorafenib, another small molecule tyrosine kinase inhibitor, was evaluated in a phase II study that included 43 patients with PNET. Patients received sorafenib 400 mg twice daily. In a preliminary analysis, 10% of patients with PNET were observed to have a partial response (Hobday et al., 2007).

Sunitinib was evaluated in a multi-institutional phase II study that included 66 patients with PNET. Patients were treated with repeated 6 week cycles of oral sunitinib (50 mg/d) for 4 weeks followed by 2 weeks off treatment. Overall, objective response rate in PNET was observed to be 16.7% . One-year survival rate was reported to be 81% in the PNET group (Kulke et al., 2008). Based on encouraging results from this study, a phase III trial to confirm the activity of sunitinib was undertaken. Patients were randomized to receive once daily oral sunitinib at a dose of 37.5 mg or matching placebo. After enrollment of 171 patients, the data safety monitoring committee recommended the discontinuation of study and accrual was stopped before the preplanned efficacy analysis. The discontinuation of the study precluded definitive hypothesis testing for progression free survival difference between the two arms. An analysis of the enrolled patients, 86 of whom received sunitinib and 85 of whom received placebo, showed that the median progression free survival was significantly longer with sunitinib compared to placebo (11.4 months vs. 5.5 months ; hazard ratio= 0.42; $p < 0.001$). The objective response rate was 9.3% in the sunitinib group vs. 0% in the placebo

group. At the data cut off point, the hazard ratio of death was 0.41 (95% CI, 0.19-0.89; P=0.02), with 10% of deaths reported in the sunitinib arm compared with 25% of deaths reported in the placebo arm (Raymond et al., 2011a). Grade 3/4 adverse events were uncommon in the treatment arm with the most common being neutropenia (12%) and hypertension (10%). Updated results, however, showed continued favorable trend for overall survival in the sunitinib arm but without statistical significance, with a hazard ratio of 0.737 (95% CI 0.465- 1.168; p=0.1926) (Raymond et al., 2011b). Based on this trial, FDA approved sunitinib for advanced PNET in May, 2011.

10.2 Targeting mTOR pathway

mTOR is an intracellular protein kinase which regulates cellular response to nutrients and energy in addition to mediating signaling through downstream growth factors such as insulin-like growth factor (IGF-1).Sporadic neuroendocrine tumors are known to co-express both IGF-1 and its receptor. There is in vitro evidence suggesting stimulation of mTOR pathway and inhibition of this pathway has demonstrated tumor regression in preclinical models (von Wichert et al., 2000; Yao, 2007). Temsirolimus and everolimus are rapamycin derivatives that have been tested in PNET. Temsirolimus was evaluated in a phase II clinical trial in advanced neuroendocrine tumors which included 15 patients with PNET. Partial response rate of 6.7% was observed in the PNET patient population (Duran et al., 2006). In an initial phase 2 study the combination of everolimus and octerotide was evaluated, reporting a partial response of 27% in patients with PNET (Yao et al., 2008b). The activity of everoliumus was subsequently evaluated in an international phase II multicenter trial (RADIANT-1). A total of 160 patients with advanced PNET were enrolled into the study. In this non randomized study, treatment with everolimus was associated with an overall response rate of 4.4% and progression free survival duration of 16.7 months in patients receiving concomitant octerotide. In patients not receiving octerotide, the response rate was 9.6% and progression free survival duration was 9.7 months (Yao et al., 2010a). This was followed by an international phase III randomized clinical trial (RADIANT 3) assigning 410 patients to receive treatment with everolimus or placebo. Everolimus was administered as 10 mg once daily, in conjunction with best supportive care. Octreotide was given at the discretion of the investigator. More than 80% of patients had well differentiated disease and more than 90% had metastases to liver. The median progression free survival as assessed by the local investigator was 11 months in the everolimus group as compared to 4.6 months in the placebo arm (hazard ratio 0.35; 95% CI 0.27-0.45; p<0.001). Grade 3/4 adverse events were rare in the treatment group which included anemia (6%) and hyperglycemia (5%). The overall tumor response rate associated with everolimus in this study was 5% (Yao et al., 2011). Based on this trial, the FDA approved everolimus for advanced PNET in May, 2011.

11. Combination strategies

Strategies to combine biological agents have begun in patients with advanced PNET. In a phase II trial, the combination of everolimus and bevacizumab was recently shown to be well tolerated and associated with an overall response rate of 26% in low to intermediate grade neuroendocrine tumors (Yao et al., 2010b). CALGB 80701 is currently randomizing patients with advanced PNET to receive either treatment with everolimus or everolimus + bevacizumab, to asses efficacy and toxicity. This trial will hopefully shed more light on the role for combination strategy in the treatment armamentarium for PNET.

12. Conclusions

PNETs are a heterogeneous group of rare tumors with a wide range of biological activity, manifestation and variable prognosis. Accurate clinical, pathologic and histologic diagnosis is an important first step in developing an appropriate management plan. PNETs should be considered separately from carcinoid tumors as they are dissimilar in clinical behavior, response to treatment and prognosis. Surgical resection remains the mainstay of treatment for early stage disease. Advanced PNET often requires a multidisciplinary approach. Options for advanced stage include liver directed therapies including surgery and radioembolization techniques. Systemic treatment option include somatostatin analogs for symptom control, cytotoxic chemotherapy (temozolomide or streptozocin based regimens) and molecularly targeted agents (sunitinib and everolimus). No specific treatment sequence currently exists. Future studies will provide more insight into combination strategies and expand our treatment options for patients with this disease.

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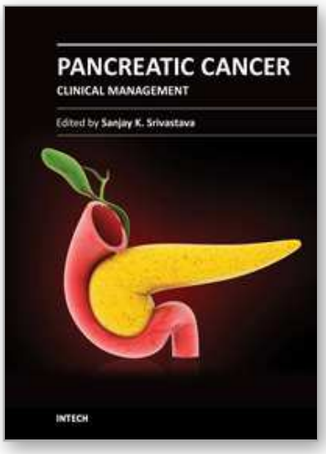

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This book covers pancreatic cancer risk factors, treatment and clinical procedures. It provides an outline of pancreatic cancer genetic risk factors, biomarkers and systems biology for the better understanding of disease. As pancreatic cancer suffers from lack of early diagnosis or prognosis markers, this book encompasses stem cell and genetic makers to identify the disease in early stages. The book uncovers the rationale and effectiveness of monotherapy and combination therapy in combating the devastating disease. As immunotherapy is emerging as an attractive approach to cease pancreatic cancer progression, the present book covers various aspects of immunotherapy including innate, adaptive, active, passive and bacterial approaches. Management of anesthesia during surgery and pain after surgery has been discussed. Book also takes the reader through the role of endoscopy and fine needle guided biopsies in diagnosing and observing the disease progression.

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