Pancreatic Neuroendocrine Tumors: Case Reports on Treatment

Abstract

Pancreatic neuroendocrine tumors are relatively uncommon lesions that arise in the endocrine cells of the pancreas. There is variability in the molecular biology of these tumors, making them difficult to treat. Until recently, there have been few systemic treatment options. With the growing incidence of pNETs, multiple clinical trials are underway to determine the route of treatment that will be most beneficial. Surgical resection, especially parenchymal-sparing procedures, are being tested as well as multiple chemotherapy agents. The focus has been directed at sunitinib and everolimus as chemotherapy agents. These agents have shown clear clinical benefits, including increasing the progression-free survival substantially. The case reports presented will describe multiple treatment options for pNETs, as well as the results of the clinical trials.

Introduction

Pancreatic Neuroendocrine Tumors (pNETs) are heterogeneous, malignancies that make up 1-2% of pancreatic neoplasms. With an incidence of 1 per 100000 individuals within the United States every year, pNETs are rare; however, the frequency of diagnosing these tumors has increased in the past two years due to advanced, state-of-the-art technology and science.\(^1\)\(^-\)\(^3\) Compared to adults, children are seldom diagnosed with pNETs. Individuals ranging anywhere from 50 to 70 years of age are more commonly associated with them. Even with improvements made in diagnosing pNETs, they are well known for being unresponsive and resistant to current chemotherapy as a result of their diverse clinical presentation.\(^1\)\(^,\)\(^2\) Research is ongoing to define the molecular biology of pNETs, and the results have endorsed new therapies such as sunitinib and everolimus.

Prognosis of pNETs depends immensely on the differentiation of the tumor. The individuals with well-differentiated pNETs have an average life expectancy of 27 months. Those with a more aggressive disease have a poorer prognosis, and are associated with poorly-differentiated pNETs.\(^1\)\(^,\)\(^3\) The only probable cure, as of late, is surgical resection. Surgical resection is only beneficial on small lesions that have yet to metastasize. However, multiple case
studies have been done to eliminate surgical resection and promote parenchymal-sparing surgery. These studies include endoscopic ultrasound (EUS) guidance for fiducial placement and new chemotherapy regimens. Currently, there are multiple approaches for the treatment of pNETs.

**Neuroendocrine Tumor Overview**

The neuroendocrine system is composed of cells that have characteristics comparable to nerve cells and hormone-producing endocrine cells. These cells are dispersed throughout the body within certain organs such as the lungs, appendix, small intestine (duodenum), rectum and pancreas. Neuroendocrine cells can develop into tumors, many of which grow slowly and others that can be very aggressive and spread to other parts of your body. The contents of the cells that compose these tumors, like the cytoplasm, contain an array of hormones and biogenic amines. These substances are released and circulated throughout the body and can result in syndromes associated with tumors.

Neuroendocrine tumors (NETs) generally bring about a diagnostic and therapeutic challenge for those involved in the treatment. These tumors have a broad range of symptoms due to the fact that they can develop in multiple organs. This broad range of symptoms makes these malignancies tough to recognize at an early stage; therefore, a majority of NETs are diagnosed at advanced stages. It is custom to term the type of NET according to the organ or type of cell that it develops in. There are multiple forms of NETs such as, carcinoid tumors of the lung or intestinal tract, pancreatic neuroendocrine tumors (pNET), medullary thyroid carcinoma, and merkel cell carcinoma. The most common sites from NETs to develop are in the pancreas and intestines. Some tumors can be benign and are slow growing as opposed to cancerous NETs that are aggressive and most often result in metastases.

**RECIST Guidelines**

Assessment of tumors throughout treatment processes is an important component in studying cancer therapeutics. In February of 2000, a set of guidelines for measuring tumor response to treatment, using radiography, computed tomography (CT), and magnetic resonance imaging (MRI), was published by the European Organization for Research and Treatment of Cancer, the National Cancer Institute of the United States, and the National Cancer Institute of
Canada Clinical Trials Group. These set of guidelines are known as the Response Evaluation Criteria in Solid Tumors (RECIST). It was based off of previous models created by the World Health Organization. Using the RECIST standards is not required, but many find it beneficial to measure disease. The RECIST model recognizes four particular response categories:

- **CR (complete response)** = disappearance of all target lesions.
- **PR (partial response)** = 30% decrease in the sum of the longest diameter of target lesions.
- **PD (progressive disease)** = 20% increase in the sum of the longest diameter of target lesions.
- **SD (stable disease)** = small changes that do not meet above criteria.

Depending on how well the disease has responded to the treatment, the tumor will be rated and placed under one of the RECIST categories. With improvements made with modern technology, specifically in PET/CT, the RECIST model is constantly being revised. In regards to treatment processes, especially clinical trials, RECIST has been widely accepted as a standardized measure of tumor response.

**Pancreatic Neuroendocrine Tumor Classification/Types**

Pancreatic neuroendocrine tumors can be classified and broken down in a couple of different ways. To begin with, these tumors are either labeled functioning or non-functioning pNETs depending on the characteristic symptoms and hormones produced. They can also be broken down into well-differentiated and poorly differentiated pNETs.

**Class I: Functional pNETs**

Tumors that produce and secrete hormones are known as functional pNETs. The hormones released cause symptoms within the body, helping with an early diagnosis of these tumors. Functional tumors produce and secrete hormones such as, gastrin, insulin, and glucagon. The type of hormone released helps to further divide pNETs. They are classified by the type or hormone that is secreted. Functional pNETs are generally slow-growing and benign. They do have the ability to be cancerous, but are uncommon.

Insulinomas, the most common form of functional pNETs, secrete an excessive amount of insulin, lowering the blood sugar levels within the body. Insulinomas are most often benign. Some of the symptoms associated with insulinomas are headaches, confusion, eyesight changes,
and weakness. They can be found in any portion of the pancreas, but are small and hard to find.\textsuperscript{11,13} Gastrinomas are another functional pNET, and secrete above average levels of gastrin. High levels of gastrin can cause ulcers within the stomach and small intestine and diarrhea. Most gastrinomas are malignant or have the ability to become malignant.\textsuperscript{11,16} They are most commonly located in the head of the pancreas, but have been diagnosed in the duodenum.\textsuperscript{13} Glucagonomas, another functional pNET, are often malignant. They are a form of pNET that overproduces glucagon, raising the blood sugar level to dangerous levels. Hyperglycemia is the cause of many symptoms of glucagonomas. These tumors usually form within the body or tail of the pancreas and are large in size.\textsuperscript{11,13,16}

\textbf{Class II: Non-functional pNETs}

Non-functional pNETs are tumors that secrete hormones but do not induce symptoms. Around 90\% of these tumors are malignant; however, they only account for 30\% of pNETs. Non-functioning pNETs are most often diagnosed in late stages with mass effects. Individuals with these tumors are generally diagnosed due to mechanical complications from tumor growth.\textsuperscript{11-13,16} These tumors require treatment as soon as possible due to malignancy. Metastases can happen anywhere, but generally appears within the liver (see Figure 1). Another name for non-functional pNETs is islet cell tumors.\textsuperscript{12,14,16}

\textbf{Differentiation}

The differentiation of the tumors also contributes to the classification of pNETs. They can either be well-differentiated or poorly differentiated. The differentiation is determined by the size, shape, and aggressiveness of the tumor.\textsuperscript{1,3,12,15} Well differentiated tumors are generally considered low grade, while poorly differentiated tumors are considered high grade. The classification of pNETs is crucial because it determines what treatment plan the individual will undergo.\textsuperscript{22}

\textbf{Treatment and Prognosis}

The spectrum of available treatments is increasing due to the rising incidence of pNETs. Options for treatment include surgical resection, radiotherapy, and chemotherapy.\textsuperscript{2,17,18} Tumors that have been caught early, before mass metastases, are often treated with surgical management. Attempts must be made to surgically remove small lesions as long as there is an absence of
distant metastases or significant comorbidity. Individuals presenting with liver metastases may benefit from hepatic resection as well. Radiotherapy can be used for palliative care, to control symptoms associated with the tumor. Advanced, unresectable pNETs are commonly managed with a chemotherapy regimen.\textsuperscript{2,3,17} Prior to 2011, the only chemotherapy agent approved to treat pNETs was streptozocin. After much research, in 2011 clinicians found 2 targeted agents that demonstrated progression in treatment, everolimus and sunitinib. Recent studies have reported that both of these agents have shown an improved progression-free survival in patients with advanced pNETs.\textsuperscript{17} Despite recent advances and earlier diagnosis, disease progression is still experienced. The only effective cure is surgical resection, and with so many cases diagnosed during late stages, surgery is not an option. As of late, the chemotherapy agents are not curative.\textsuperscript{3} Individuals with pNETs have a median survival rate of 24 months.\textsuperscript{2,17,20} Clinical trials are currently underway to determine the best approach in treating these tumors. The following case reports provide information regarding these current clinical trials.

**Case Report A: EUS-F Placement for Enucleation**

Due to the increased use of abdominal imaging, and improved quality, the detection of small pNETs has increased. “Patients with these small tumors are ideal candidates for pancreatic-sparing procedures such as enucleation that allow for greater preservation of pancreatic tissue and function than more extensive procedures such as pancreatectomy or distal pancreatectomy.”\textsuperscript{19(p.3922)} Despite the benefits, smaller lesions can be hard to pinpoint for the enucleation procedure. With the help of endoscopic ultrasound (EUS) guidance to place fiducials, these small lesions can be localized for parenchymal-sparing surgery.

A study directed by Law et al\textsuperscript{19} from September 2012 to November 2012, compared EUS and fiducial deployment in 2 consecutive patients. The purpose of this study was to gauge the efficacy, safety, and feasibility of using EUS-F for localization of pNETs.

Two female patients, with lesions of different measurements, underwent endoscopic ultrasound fiducial placement (EUS-F). The first patient, a 61-year-old female with a tumor measuring 7.4-mm, had 2 Visicoil fiducials placed and underwent surgery 14 days later. With the use of intraoperative ultrasound the lesion was identified and enucleation was performed. The same procedure was performed on a 50-year-old female with a 9.0-mm lesion. Enucleation was performed in surgery 11 days after the EUS-F. The fiducials were implanted without any
difficulties in both cases with the use of EUS. During surgery, the fiducials were distinctly visible using intraoperative ultrasound, allowing for successful enucleation of both the tumor and the fiducial (see Figure 2). “No complications were associated with EUS-F, and no evidence of pancreatitis was shown either clinically or on surgical pathology.” The 2 patients were contacted following the procedure and neither of them reported any post-procedure complications.

Fiducials reflect the precise location of the tumor and ultrasound waves, making the procedure quick and efficient for intraoperative ultrasound. Larger studies involving fiducial placement in pancreatic tumors have been done without any complications. EUS-F placement is deemed a successful, feasible and safe technique for patients with small pNETs. Patients with these small lesions that would benefit from a parenchymal-sparing procedure should be considered for this new interventional function of ultrasound.

Case Report B: CAPTEM Regimen

Chemotherapy regimens that have been used in the past, such as streptozocin based agents, come with multiple side effects, one of the worst being toxicity. A few trials were completed using temozolomide in combination with other agents. Data from the trials suggested it should be combined with capecitabine. Saif et al20 compiled the data from these previous trials of such chemotherapy agents and used the information for a new regimen of capecitabine and temozolomide (CAPTEM). The authors’ objective was to report on the efficacy and safety of using the new CAPTEM regimen.

A retrospective chart review was conducted in which 7 patients (4 males and 3 females) with metastatic pNET and progressive cancer were studied. The 7 patients did not respond to previous chemotherapy treatments and were set up with the CAPTEM regimen. The charts provided the age, sex, diagnoses, dose of CAPTEM, and the CT scan results. The patients were treated between 2006 and 2013. “Patients received capecitabine at a flat dose of 1,000 mg orally twice daily on days 1-14 and temozolomide 200 mg/m2 in 2 divided daily doses on days 10-14 of a 28-day cycle.” After each cycle, the serum tumor markers were measured, and every 2 cycles images were obtained. Each patient’s response to the CAPTEM was evaluated and graded according to the level of toxicity and RECIST guidelines. The patients seemed to tolerate the CAPTEM fairly well, with only grade 3 and 4 toxicities, and a response rate of 71% for
stable disease. The average survival time continued to be 24 months; however, three patients are still living.

The overall benefit from the CAPTEM regimen is the toxicity profile. CAPTEM is superior to other chemotherapy regimens due to the decreased side effects. “Our unique dosing of CAPTEM resulted in a well tolerated oral regimen with a good safety profile in this retrospective review.”

Future studies should be done to further evaluate CAPTEM and temozolomide monotherapy, as well as a study to compare temozolomide versus streptozocin-based regimens. These studies will help establish a standard or care for this deadly disease.

**Case Report C: Everolimus**

Research is ongoing to define the molecular biology of pNETs, and the results have endorsed new therapies for these tumors, including everolimus treatment. Recent clinical studies have shown the effectiveness of everolimus as a treatment option. Yao et al. reviewed published data from 2 phase II trials and 1 phase III trial of oral everolimus agents for the treatment of patients with advanced pNET. Everolimus is a mammalian target of rapamycin (mTOR) inhibitor that blocks the signal transduction in tumor cells and cells that play a role in tumor angiogenesis.

In the first phase II study, patients with or without progressive disease were treated with 30 mg octreotide intramuscularly and 5 or 10 mg of everolimus orally. Every 12 weeks the patients were monitored by multiphasic CT or MRI. Patients receiving the 10 mg dose demonstrated a superior response rate and an average progression-free survival (PFS) of 11.6 months. The second phase II study, RADIANT-1, involved patients with advanced pNET with progressive disease, some undergoing octreotide and everolimus and others just everolimus. The outcome of this phase indicated the patients that underwent octreotide and everolimus had a higher average PFS. The phase III trial, RADIENT-3, was a double-blind study controlled by a placebo, involving 410 patients with pNET. Patients were randomly assigned everolimus or the placebo. Those assigned the everolimus treatment exhibited a better PFS, as well as reduced hormone secretion from the tumor, than those receiving the placebo. The authors point out that the placebo effect did play an important role in the trial by allowing for the opportunity to examine the pattern of failed treatments.
The data reviewed by Yao et al\textsuperscript{21} suggests that the everolimus treatment delays tumor progression. “Recent years have seen significant improvement in our understanding of the molecular biology underlying genetic cancer syndromes involving pNET and the somatic mutations associated with sporadic pNET.”\textsuperscript{21} Efforts are underway to improve the efficacy of everolimus in pNET treatment. Ongoing clinical studies involving the use of everolimus with drugs that balance hormones are currently providing valuable information. The data from these trials provides alternatives for tumor management. Everolimus is a worthwhile treatment that should be further considered by patients with advanced, progressive pNET.

**Case Report D: Sunitinib**

Tyrosine kinase receptors play a key role in controlling cell proliferation in pNETs. Sunitinib is an oral tyrosine kinase inhibitor that blocks activation of angiogenesis. It is a potent inhibitor that stops cell proliferation. Sunitinib has been approved in many nations as a treatment option for unresectable pNETs or metastatic disease.\textsuperscript{22} It has significantly reduced endothelial cell density as well as considerably reduced blood flow and tumor volume. A series of studies and clinical trials have been compiled, examining individuals with rare pNETs. These studies evaluated the safety and efficacy of sunitinib.\textsuperscript{22,23}

During a phase I study of dose-escalation, sunitinib showed strong antitumor activity. Following the RECIST guidelines, 2 out of the 3 patients involved in the study achieved a PR to the agent, with the other individual achieving a sustained SD. A phase II study was conducted to evaluate the effects of sunitinib in advanced pNETs. The trial included 107 individuals, in which 66 had advanced pNETs and 41 had carcinoid tumors, which were set up on a specific schedule of 50 mg/day, 4 weeks on and 2 weeks off. Based on the RECIST criteria those with pNETs achieved SD for over 6 months.\textsuperscript{22}

Another study reported 2 successful uses of sunitinib on 2 separate patients. The first individual, a 12-year-old boy with metastatic disease, was treated with 37.5 mg/day, which resulted with a confirmed PR based on RECIST. The response directly correlated with decreased biochemical markers and a remarkable improvement in quality of life. The second patient also had metastatic disease and was given 50 mg/day, 4 weeks on and 2 weeks off. Under RECIST criteria, the individual achieved a CR, with all of the lesions disappearing. They also experienced normalization of biochemical markers.\textsuperscript{22}
Targeted therapy sunitinib has proven efficacy through many clinical studies. It has helped maintain quality of life for many individuals with advanced metastatic disease. Under RECIST guidelines, the studies have shown a response to the agent. More studies involving biochemical markers in measuring response to sunitinib may be effective for future treatments.

**Conclusion**

With the occurrence of 1 every 100000 people, pNETs are a rare tumors; however, with state of the art technology, they are being diagnosed more frequently every day. Due to this increase, the spectrum of treatment options has significantly grown. Becoming more aware of the classification of these tumors has also aided in selecting the regimen that will be most beneficial. Surgical resection using EUS, to spare tissue, is an interventional procedure that should be considered more often for those qualified. It is both feasible and safe. For unresectable pNETs, new target therapy innovations have revolutionized the treatment options for individuals. The approval of everolimus and sunitinib represents a huge contribution to the medical field. Individuals are seeing a more positive response with these new agents. Continuing the research into these therapies will not only aid in the treatment of pNETs, but also improve the quality of life for those individuals diagnosed with this deadly disease.
References


Figure 2. Second patient: 50-year-old woman. A. EUS image of the pancreas. B. EUS-F image. Fiducial can be located directly below the red arrow. C. Fiducial can be see on intraoperative ultrasound image. It can be located directly below the red arrow. D. Removed masses with fiducial placed within it. Image courtesy of Law JK, Singh VK, Khashab MA, et al. Endoscopic ultrasound (EUS)-guided fiducial placement allows localization of small neuroendocrine tumors during parenchymal-sparing pancreatic surgery. Surg Endosc. 2013;27(10):3921-3926.