Neuroendocrine Tumours of the Pancreas
Understanding the symptoms, diagnosis and treatment options
by Dr Liau Kui Hin

Pancreatic neuroendocrine tumours (PNETs), unlike pancreatic adenocarcinoma, have distinctly different tumour biology. The spectrum of biologic behaviour ranges from indolent to aggressive and benign to malignant. By and large, PNETs are a diverse group of cancers and account for less than 3% of all pancreatic tumors. In recent years, with greater public awareness and widespread use of CT scan imaging, more PNETs are diagnosed incidentally.

These cancers arise from the endocrine cells in the pancreas. The pancreatic endocrine cells are also known as islet cells. These cancers can be hormone secreting or non-hormone secreting. Some of these hormones are active or functional and they cause hormone-related symptoms while others are inactive or non-functional. The majority of PNETs are nonfunctional tumours. Non-functional PNETs are generally asymptomatic in the early stage and at the time of diagnosis, they are often in the advanced stage. Examples of the hormones secreted by the tumours are insulin, glucagon, vasoactive intestinal peptide, gastrin and somatostatin. By the nature of hormones they produce, PNETs are also known as insulinoma, glucagonoma, gastrinoma, VIPoma, PPoma and somatostatinoma. Table 1 describes the different types of pancreatic neuroendocrine tumors, the hormones that they produce and presenting symptoms.

### Table 1. Types of pancreatic neuroendocrine tumours, the hormones that they produce and presenting symptoms

<table>
<thead>
<tr>
<th>PNETs Type</th>
<th>Hormones</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulinoma</td>
<td>insulin</td>
<td>Neuroglycopaenia symptoms (e.g. lethargy, giddiness, blurring of vision)</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>gastrin</td>
<td>Gastric ulcer May be associated with MEN Syndrome</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>glucagon</td>
<td>May present with skin rash (necrolytic migratory erythema)</td>
</tr>
<tr>
<td>VIPoma</td>
<td>VIP</td>
<td>Watery diarrhea, hypokalemia and achlorhydria</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>somatostatin</td>
<td>Steatorrhoea</td>
</tr>
<tr>
<td>Pancreatic Polypeptidomas (PPoma)</td>
<td>pancreatic polypeptide</td>
<td>Change in satiety</td>
</tr>
<tr>
<td>Non-functioning tumour</td>
<td>inactive hormones or none</td>
<td>Mass effects of tumour</td>
</tr>
</tbody>
</table>
Presenting symptoms

PNETs may be symptomatic or asymptomatic. Majority of patients with PNETs are asymptomatic, especially the non-functioning PNETs. Those patients with PNETs related symptoms are often non-specific. It is therefore not surprising that proper diagnosis is frequently delayed for a long time. On the other hand, functioning PNETs may have symptoms related to the hormones that are secreted by the tumour [Table 1]. For instance, patients with insulinoma may have classic Whipple’s triad or hyperinsulinemic-hypoglycaemic syndrome, patients with gastrinoma may present with Zollinger-Ellison syndrome and patients with VIPoma are associated with watery diarrhea, hypokalaemia, hypochlorhydria and acidosis (WDHHA) or Vernal Morrison Syndrome.

Nonfunctional tumours do not produce any hormones so they do not cause any hormone-related symptoms. As a result, these tumours are typically diagnosed once the tumour is advanced and is causing mass effect related symptoms such as pain or jaundice or gastric outlet obstruction.

Confirmation of diagnosis

Guided by the presenting symptoms, a combination of laboratory tests, radiological and nuclear imaging and tumour tissue analysis are carried out. Diagnosis of PNETs may be suspected by biochemistry tests using specific and non-specific PNETs tumour markers. Serum chromogranin A is a useful non-specific general biomarker for the diagnosis of neuroendocrine tumour. Neuron-specific enolase (NSE) is an alternative tumour markers if CgA level is normal, for example in patients with poorly differentiated G3 PNETs. Other specific markers are serum insulin, glucagon, pancreatic polypeptide and gastrin.

Multiphasic CT scan helps in diagnosing and locating the tumour in the pancreas and it also allows assessment of the loco-regional extent of tumour [Figure 1]. Other imaging modalities such as magnetic resonance imaging (MRI), trans-abdominal ultrasonography, endoscopic ultrasonography and positron emission tomography (PET) scan may be useful to diagnose and assess the presence of tumours.

Although PNETs can be confirmed by Ga-Doctatate PET scan, histological diagnosis from a biopsy of the tumour with immuno-histochemistry analysis remains the precise standard. Biopsy of tumour tissues can be obtained via endoscopy using image-guided approach such as endoscopic ultrasonography or CT scan guided percutaneous approach. Fluoro-deoxy-Glucose (FDG) PET scan may be ordered to assess the activity of the tumours. Histological analysis of the cell types, the differentiation and grade of tumours (Grade I to Grade 3 based on the mitotic count and Ki67 index) together with the stage and extent of tumour from radiology are crucial information for the oncologists. Not only it helps to formulate the treatment plan for the patient, it also guides the prognosis of PNETs.

Hereditary tumour syndromes in PNETs

While majority of the PNETs are sporadic in occurrence, some occur in a genetic setting. PNETs can occur in multiple endocrine neoplasia syndrome (MEN) and Von Hippel-Lindau (VHL) syndrome. When there is positive family history of pancreatic, parathyroids and pituitary disease or PNETs in young patients, MEN syndrome has to be considered. Currently, genetic test to analyse the menin gene mutation confirmed the diagnosis.

Prognosis

The prognosis of PNETs is dependent on the stage of tumour at diagnosis. The 5-year overall survival rates for patients with non-functioning PNETs are estimated between 26% to 58%. Localized PNETs that can be completely removed by surgery have excellent prognosis and this group of patients enjoys long-term survival. In patients with liver metastasis, the overall 5-year survival rate ranges from 20% to 38%.

Treatment options

The optimal treatment goals for pancreatic neuroendocrine tumours are firstly, to control hormone and tumour related symptoms, if present, and secondly, to improve long-term survival by extirpating the tumours completely. Depending on the stage of PNETs, a variety of therapeutic options are available for both, symptoms and tumour controls.

Surgery

In general, surgery to remove the tumour completely remains the mainstay for early stage PNETs unless the patient is not fit for an operation. Surgery is the only modality of treatment that can achieve both treatment
goals satisfactorily. For example sporadic insulinoma, surgery can achieve a cure rate of more than 90% of the patients. Depending on the location and extent of the tumours, pancreas surgery may differ in the approach and techniques. Pancreatic surgery includes enucleation of tumour, segmental pancreatectomy, Whipple’s operation (pancreaticoduodenectomy), pylorus preserving pancreaticoduodenectomy and subtotal distal pancreatectomy. Some of these operations can be performed by laparoscopic technique with the advantages of smaller skin incisions, faster recovery and shorter hospitalisation. In hospitals with specialized centres in hepatobiliary and pancreatic surgery, these operations can be performed with lower complications and mortality rates.

In selected patients with advanced PNETs where the tumour is limited to liver involvement, surgery to remove liver metastases may be beneficial. Complete removal of pancreas and its metastases, or safe removal of as much as 70% to 90% of pancreatic tumour bulk can ameliorate disease symptoms and prolong survival. With less tumour bulk and hormones secretion, medical therapy may be rendered more effective in controlling the residual tumour.

Orthotopic liver transplantation is an option for a few highly selected cases where there is liver-only metastasis, unresponsive or exhausted all medical therapy. Aggressive PNETs is usually contraindicated for liver transplantation.

Liver directed interventional therapy
When liver is the only site of metastasis in patients with advanced PNETs and are not fit for an operation, other options available include radiofrequency ablation, transarterial embolisation or chemoembolisation and radioactive isotope yttrium-90 (90Y) radioembolisation therapy. Radioactive isotope yttrium-90 (90Y) radioembolisation is also known as selective internal radiation therapy (SIRT). These modalities of treatment can be combined with systemic chemotherapy or molecular therapy.

Hormonal therapy
Somatostatin analogues have been proven to control symptoms by reducing and blocking the hormones production by the tumour and in addition, it has anti-proliferative effects to control progression of the tumour. Clinical response in term of hormone related symptoms can be significant in PNETs such as VIPoma and glucagonoma. In well-differentiated PNETs, somatostatin analogue is recommended as the first-line medical therapy. Poorly differentiated grade 3 PNETs may be resistant to this therapy because of the absence of somatostatin receptors.

The somatostatin analogues available are octreotide, lanreotide and pasireotide. The effects are achieved by blocking the somatostatin (sst) receptors on cell surface. There are five subtypes of sst receptors (sst1 to sst5). Octreotide and lanreotide preferentially bind to sst2-receptor and have moderate affinity for sst3 and sst5 receptors while pasireotide blocks more somatostatin receptors (sst1, sst2, sst3 and sst5) and also has higher affinity for sst5 than octreotide. In metastatic grade 1 and 2 non-functional PNETs, lanreotide has been shown to prolonged progression-free survival. Furthermore, these somatostatin analogues have favourable safety and adverse effect profile.

Systemic chemotherapy and molecular therapy
Patients diagnosed with metastatic Grade 2 (G2) PNETs and Grade 3 (G3) PNETs chemotherapy is recommended. Systemic cytotoxics are also recommended in patients with inoperable progressive liver metastasis in Grade 1 (G1) or Grade 2 (G2) PNETs. The cytotoxic drugs include cisplatinum, etoposide, streptozotocin and 5-fluorouracil (5-FU) or doxorubicin. Other agents that have anti-tumour effects with good tumour response are temozolomide and capecitabine. Anti-VEGF agents (e.g. bevacizumab) may be added to the chemotherapeutic regimen because of the characteristic hypervascularity in PNETs [Figure 2].

Tyrosine kinase inhibitors are used to treat PNETs. Two targeted agents, pazopanib and sunitinib, have been studied and shown to be effective in controlling the progression of advanced PNETs. Other targeted agents, such as mTOR-inhibitors (e.g. everolimus) also have significant anti-tumour effect.
Interferon immunotherapy

Interferon alpha therapy is one of the treatment options for patients with functioning PNETs and low proliferation.20 It controls symptoms and tumour proliferative activity effectively. However, interferon is less attractive because of its side effects and safety profile.21 For that reason, it is usually used as second line therapy. Fever, fatigue, anorexia and weight loss are common. Interferon therapy can be combined with somatostatin analogues to achieve a synergistic effect in symptoms and tumour control.

Radionuclide targeted therapy

Radionuclide targeted therapy is also known as peptide radionuclide receptor therapy (PRRT). This is a beta-emitter labeled somatostatin analogue which delivers a lethal radiation dose to the tumour cells. PRRT is a relatively novel therapy that was added to the therapeutic armamentarium of PNETs.22 Only PNETs with abundant somatostatin receptors are indicated. Bone marrow and renal toxicities are the main concern in this therapy. Although good response rate and tumour stabilisation have been reported, further studies to clarify its validation are needed.24

Evidence based treatment excellence

The myriad of treatment options available for PNETs emphasises the fact that there isn’t any one best option when treating the family of cancers in PNETs. Furthermore, different therapies discussed earlier are at different stages of their scientific studies and understandings. Some therapies are supported by high quality of scientific evidence and some are still considered investigational while others are waiting for more data from randomised control trials. A multi-disciplinary team with all the relevant expertise in managing PNETs is important in delivering treatment excellence. The best clinical decisions are the product of good clinical judgment informed by high quality of medical sciences from various relevant disciplines. Comprehensive assessment and treatments require advanced diagnostic and therapeutic medical technology, professional expertise and modern medicine. Treatment plan should be strategised with longitudinal consideration for possible treatment failure or therapy tolerance.

Follow-up review

Patients diagnosed with PNETs are recommended to have regular medical review at an interval between 3 to 6 months. The more aggressive grade 3 PNETs is recommended to have closer review between 2 to 3 months interval. During each review, serum chromogranin A, relevant tumour markers and appropriate imaging are performed to survey for tumour recurrence or tumour progression. FDG PET scan or dual-tracer PET scans may be indicated. Repeat biopsy of the liver metastases may be necessary to reassess the proliferative activity of the tumour when it progresses rapidly or fails therapy.

Conclusion

With the advances in medical sciences, the spectrum of PNETs’ treatment options has expanded tremendously in the recent years. Surgical oncologists, medical oncologists, endocrinologists, pathologists, nuclear and radiation oncologists working collaboratively in a multi-cum trans-disciplinary team is undoubtedly the best way to deliver treatment excellence. Future research and clinical trials will provide better understanding in cellular and molecular biology of these heterogeneous tumours, and possibly leading to breakthrough innovative treatment strategy in PNETs.25

References:


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