BACKGROUND

NEUROENDOCRINE cells are located throughout the body. They release hormones in response to a variety of stimuli to regulate a wide range of normal physiological functions. Neuroendocrine tumours (NETs) arise from this diverse group of cells and are most commonly found in the gastrointestinal tract and pancreas.

Although these tumours share common markers of neuroendocrine differentiation, they have different embryological origins and extremely variable biological behaviour, ranging from benign to very aggressive tumours. Some NETs secrete hormones that can cause significant morbidity and be life-threatening despite their slow growth. By contrast, some patients with very slow-growing tumours survive for many years, even in the presence of metastatic disease.

In the past decade there have been multiple advances in biochemical, histopathological and imaging techniques, resulting in improved diagnosis, classification and accuracy of prognosis. These advances are enabling a new era of personalized medicine in which a number of new targeted therapies can be selected for an individual patient, leading to improved patient outcomes.

Epidemiology

Although uncommon, the incidence of NETs has risen significantly over the past few decades, and NETs now constitute the second most prevalent GI tumour after colorectal cancer. Improved awareness combined with advances and better availability of imaging, biochemistry and endoscopic techniques has almost certainly contributed to this rise. Therefore, it is difficult to discern if there has been a true increase in tumour incidence.

Most NETs are sporadic but some are observed in high frequency in inherited familial syndromes, including multiple endocrine neoplasia (MEN), von Hippel-Lindau disease and neurofibromatosis. In sporadic cases we have noted a disproportionately high number of patient referrals from non-metropolitan areas and further research is needed to elucidate potential carcinogens.

The authors

DR MICHAEL HOFMAN, nuclear medicine physician, centre for cancer imaging, Peter MacCallum Cancer Centre, and clinical senior lecturer, University of Melbourne.

ASSOCIATE PROFESSOR MICHAEL MICHAEL, medical oncologist, head of upper GI tumour stream, Peter MacCallum Cancer Centre, and co-chair, neuroendocrine service, and associate professor of medicine, University of Melbourne.

MR BENJAMIN THOMSON, hepatobiliary surgeon, Peter MacCallum Cancer Centre, and head of upper GI tumour stream, Royal Melbourne Hospital.

PROFESSOR RODNEY HICKS, department of medicine and radiology, University of Melbourne, and director, centre for cancer imaging; co-chair, neuroendocrine service and translational research group; and head, molecular imaging and targeted therapeutics laboratory, Peter MacCallum Cancer Centre, Melbourne.

Neuroendocrine tumours

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2011 How to Treat Yearbook

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Neuroendocrine tumours

Classification and pathology

NETs can be classified according to the site of origin and the degree of differentiation and function.

Site

Traditionally, NETs were classified by site of origin:
- Gut (including stomach, small intestine, colon, rectum, appendix, pancreas)
- Pancreas
- Lung
- Breast
- Other sites

Degree of differentiation and function

NETs can be divided into well-differentiated or poorly differentiated categories, which characterise disease biology and prognosis and enable appropriate selection of treatment (table 1). There is, however, a continuum between the two, and moderately differentiated tumours may have characteristics of either group and thus be less predictable in terms of clinical behaviour.

Table 1: Spectrum of NETs, from well to poorly differentiated

<table>
<thead>
<tr>
<th>GRADE (NETs)</th>
<th>Ki-67 index</th>
<th>Functional imaging</th>
<th>Octreoscan SPECT of SSTR PET/CT</th>
<th>Prognosis</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well differentiated</td>
<td>≤2</td>
<td>Low (G1)</td>
<td>Intermediate (G2)</td>
<td>High (G3)</td>
<td>Incident (slowly growing)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>&gt;2</td>
<td>More rapid growth on serial imaging</td>
<td></td>
<td></td>
<td>Aggressive</td>
</tr>
</tbody>
</table>

Well-differentiated NETs

The cells of well-differentiated NETs closely resemble the normal neuroendocrine cell from which they arose, and the tumours tend to have slow growth with an indolent natural history.

Poorly differentiated NETs

Carcinoid syndrome

Carcinoid syndrome is a clinical syndrome caused by the secretion of excessive quantities of the amine serotonin or one of its metabolites, 5-hydroxyindoleacetic acid (5-HIAA). It follows the activation of serotonin receptors (5-HT2) on target tissues leading to characteristic symptoms.

Clinical features — symptoms and signs

<table>
<thead>
<tr>
<th>Disease</th>
<th>Hormone produced</th>
<th>Site (most common)</th>
<th>Clinical features</th>
<th>Investigations (blood)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid syndrome</td>
<td>Serotonin, others (histamine, substance P)</td>
<td>Small bowel</td>
<td>flushing, diarrhoea, abdominal pain, carcinoid heart disease (tricuspid regurgitation, right heart failure)</td>
<td>CgA, urine 5-HIAA</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>Insulin</td>
<td>Pancreas</td>
<td>Whipple’s triad (symptoms of hypoglycaemia (eg, blurred vision, sweating, tremor, weakness, confusion, coma) + glucose &lt;2 mmol/L + relief of symptoms with administration of glucose)</td>
<td>Fasting or random glucose, 72-hour fast test (requires hospitalisation)</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>Gastrin</td>
<td>Duodenum</td>
<td>Peptic ulcer, gastric reflux, diarrhoea</td>
<td>Fasting gastrin, Gastricscan/Pit-24h pH-metry Secretin test*</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Glucagon</td>
<td>Pancreas</td>
<td>Neonatal diabetes, impaired glucose intolerance or diabetes</td>
<td>Glucagon</td>
</tr>
<tr>
<td>VIPoma</td>
<td>Vasoactive intestinal peptide (VIP)</td>
<td>Pancreas</td>
<td>Profuse watery diarrhoea and resultant dehydration, hypokalaemia and achlorhydria (pancreatic cholera syndrome)</td>
<td>VIP, Hypokalaemia</td>
</tr>
<tr>
<td>Somatostatoma</td>
<td>Somatostatin</td>
<td>Pancreas</td>
<td>Triad of diabetes mellitus, steatorrhoea and gait abnormalities, also associated with hypochloraemia</td>
<td>Somatostatin</td>
</tr>
</tbody>
</table>

Table 2: Features of selected syndromes

CgA = chromogranin A
5-HIAA = 5-hydroxyindole acetic acid
VIP = vasoactive intestinal peptide
*Secretin test: administration of exogenous secretin; test is positive if serum gastrin levels increase

Result. Clinical signs included elevated jugular venous pressure with large V waves, right venricular heave, the pancytopenic marasmus of tricuspid regurgitation and a large, palpable and tender liver. Acute and oedema may also occur. The consequent hepatic congestion results in a decreased capacity of the liver to degrade hormones, which further exacerbates symptoms and can result in carcinoid syndrome.

Gastrointestinal NETs

Small bowel carcinoids are frequently asymptomatic or present with vague abdominal symptoms that can be mistaken for irritable bowel syndrome. Some patients present with intermittent or acute bowel obstruction. Production of serotonin or other bioactive amines is a typical feature of small-bowel carcinoids, and local secretion causes mesenteric fibrosis that predisposes to bowel obstruction or can compress mesenteric vessels, resulting in bowel ischaemia and malabsorption.

Most gastric, appendicular and rectal carcinoids present as incidental findings. These tumours are usually non-functional and remain asymptomatic until advanced.

Pancreatic NETs

Non-functional pancreatic NETs may grow for a long time without causing symptoms. When large enough, obstruction of bile or pancreatic ducts may cause obstructive jaundice or symptoms due to pancreatic exocrine insufficiency, such as diarrhoea.

About half of pancreatic NETs are functional, producing a range of hormones resulting in characteristic syndromes (table 2). Tumours.

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From page 34

**How to Treat**

Neuroendocrine Tumours

**Investigation** should be personalised for each patient, taking into account the likely natural history and the general health of the patient.

**Biochemical Markers**

In patients with suspicious symptoms, measurement of chromogranin-A (CgA) can be helpful, but other more complex tests are best co-ordinated by an endocrinologist, gastroenterologist or oncologist. CgA is a glycoprotein present in the secretory granules of most neuroendocrine cells. It is co-secreted along with other hormones but can be elevated in either functional or non-functional NETs. Very high levels of CgA are rarely found outside the setting of NETs. Mild or moderate elevation and consequent false-positive results may occur in patients treated with gastric acid secretory blockers, especially proton-pump inhibitors, and also in patients with impaired renal function, pregnancy, Parkinson’s disease or untreated hyperparathyroidism. If there is suspicion of a specific syndrome, tests for hormone excess are indicated (Table 2).

5-Hydroxyindole acetic acid (5-HIAA) is the urinary breakdown product of serotonin and can be measured using a 24-hour urine collection in patients with features of carcinoid syndrome. Some foods, including plums, pineapples, bananas, eggplants, tomatoes, avocados and walnuts contain high levels of serotonin, which can increase urinary levels of 5-HIAA, and should be avoided three days before collection. 5-HIAA can also be increased in patients with untreated maldigestion such as in coeliac disease. A variety of medications can also increase or decrease 5-HIAA levels. CgA and 5-HIAA are sensitive tests and are increasingly replacing use of urinary 5-HIAA.

**Imaging**

Once NET is strongly suspected on the basis of biochemical testing, or confirmed on biopsy, systemic staging is necessary, since localisation of the primary site of disease and the presence of metastases has both prognostic and therapeutic implications.

CT of the thorax, abdomen and pelvis is generally the first test but unfortunately has relatively low sensitivity for the primary tumour and will often significantly understate the extent of metastatic disease. In particular, liver metastases can be difficult to detect unless a triple-phase protocol involving pre-contrast, arterial and portal venous phase imaging is adopted. Small hepatic metastases can be most sensitively identified using 2-Tesla MRI with a hepatocyte-specific contrast agent.

Unless a primary lesion is readily apparent, specialised imaging techniques may be necessary. These include CT enteroscopy (CT combined with intraluminal radiocontrast) for small bowel lesions, and MRI or endoscopic ultrasound for pancreatic lesions. These are best arranged by specialists experienced in the management of NETs, especially oncological surgeons.

By virtue of SSTR expression in most NETs, various radio-labelled somatostatin analogues have been developed for diagnostic imaging. These have three basic components—a radionuclide that emits radiation detectable outside the body, linked via a chelating agent to a peptide that binds to the SSTR. The only commercially available and approved agent for SSTR-imaging is Indium-111 DTPA-octreotide (OctreoScan). The radioisotope is injected intravenously followed by imaging on a nuclear medicine gamma camera over the next 1-2 days. In addition to obtaining two-dimensional ‘planar’ imaging, it is now routine to obtain three-dimensional cross-sectional images by rotating the detectors around the patient, using a technique called single photon emission tomography (SPECT). Although widely available, Octreoscanning is an expensive test and quite difficult to interpret. An inherent drawback is the absence of anatomical information, precluding lesion characterisation or precise localisation, leading to difficulty distinguishing physiological or benign uptake from pathological uptake. These limitations can be overcome with hybrid SPECT-CT scanners, which provide both functional (SPECT) and anatomical (CT) information. Octreoscanning is best performed on a multi-slice SPECT-CT device and is significantly more sensitive than conventional imaging, with a large impact on patient management.

Recently, a few specialised centres have introduced SSTR-imaging combined with positron-emission tomography–CT (PET–CT) devices, using gallium-68 DOTATATE (DOTATATE, GaTate) instead of indium-111 in the radionuclide somatostatin analogues. PET provides vastly superior imaging (accurately identifying disease as small as 2-3mm) and speed (the scan can be completed in 60-90 minutes) compared with conventional gamma camera SPECT imaging. Patients in whom there is a strong clinical suspicion of NETs but who test negative on conventional imaging and Octreoscan, or patients who have Octreoscan findings suggestive of metastatic disease amenable to curative resection, should be considered for this form of scanning.

As well as more accurately defining the presence and extent of NETs, SSTR-imaging also characterises the biology of disease. As a marker of normal cellular differentiation, high uptake of Octreoscan or the PET analogues indicates that the disease is well differentiated and generally has an indolent natural history and therefore tends to be resistant to conventional oncology treatments, such as chemotherapy.

As the disease becomes de-differentiated and aggressive, there tends to be a loss of SSTR. This is an adverse prognostic indicator but does indicate a higher likelihood of benefit from chemotherapy, as detailed below. As with most aggressive tumour types, PET–CT imaging with fluorodeoxyglucose (FDG), a glucose analogue, is a sensitive means to detect and stage disease, as rapidly proliferating cells use glucose as a substrate for energy. In some patients, the combination of SSTR imaging and FDG PET–CT is indicated to characterise sites of well and poorly differentiated disease.
Management

IN patients with advanced-stage disease, early referral to a centre with multidisciplinary expertise incorporating surgical oncology, medical oncology, nuclear medicine, interventional radiology, endocrinology, gastroenterology and radiation oncology is advised. Given the complexity and heterogeneity of this disease, therapy is individualised based on several factors:

• Disease extent.
• Rate of growth determined by imaging studies and histological grade/proliferative index.
• Level of SSTR expression and FDG avidity (ie, positivity) on nuclear medicine imaging.
• Disease-related symptoms with regard to the primary lesion or metastatic deposits.
• Patient comorbidities.

Surgery

Complete surgical resection remains the only curative treatment for NETs. Unfortunately most patients present late with metastatic disease. While some pancreatic hormone-secreting tumours may be resected by partial gastrectomy, the majority tumour or metastases is appropriate for carcinoid tumours. However, small pedunculated tumours may be warranted for carcinoid syn- drome secondary to hepatic metastasis, surgical cure is still possible if complete resection of hepatic metastatic deposits can be performed. For patients in whom not all of the liver disease is resectable, symptom control is still possible if 90% of the disease can be removed or ablated. In both surgical situations (with curative or palliative intent), resection with or without ablative techniques (eg, microwave or radiofrequency ablation) can be used. For patients with extensive hepatic replacement by tumour, surgical resection is not possible. Hepatic transplantation has been used in this context but Australian guidelines do not recommend its use.

There are no current available SSTR imaging with Octreoscan (Biocytex) or SPECT-CT imaging is available in a few specialised centres but not for the SSAs. Apart from the inhibitory effects of somatostatin analogues, these agents also have an antiproliferative effect in slowing tumour growth, stabilising them radiologically in about two-thirds of patients, and inducing tumour regression in up to 10% of patients. The introduction of SSAs may be responsible for the increased survival of patients with NETs observed over the last two decades.

KEY POINTS

Diagnosis

• Chromogranin-A (CgA) is the most practical and useful general serum tumour marker in patients with NETs.

• Elevated CgA levels occur in patients on proton-pump inhibitors, but very high levels are rarely seen outside the setting of NETs.

• Somatostatin receptor (SSTR) imaging with Octreoscan SPECT-CT is more sensitive than conventional imaging for localisation and staging NETs.

• SSTR PET-CT imaging is available in a few specialised centres but can have a high false-positive rate in patients with an unknown primary site of disease (by directing to curative surgery) or in patients with metastatic disease on conventional workup before major surgical intervention (by detecting distant metastatic disease and directing away from futile surgery).

Therapy

• In patients with carcinoid syndrome, echocardiography is important to detect carcinoid heart disease.

• Tumour grading plays a key role in defining prognosis and therapeutic options.

Neuroendocrine tumours

Patients who have only had con- surgery. However, necessarily preclude consideration for curative or palliative surgery.

Most published data for surgical resection of NETs reports on patients who have only had conventional CT or Octreoscan scanning preoperatively, which, as explained above, may have under- estimated the extent of disease in those patients. The development of 3-Tesla MRI and SSTR PET-CT has significantly improved the accuracy of preoperative staging and detection of metastatic disease. Although not widely available, these should now be considered essential preoperative staging investiga- tions when resection is being considered. Cure will only be possible in patients in whom all sites of disease can be resected.

Guidelines exist to aid in deci- sion making about surgical treat- ment for the broad range of poten- tial sites involved with tumour. Gastric tumours are usually resected by partial gastrectomy, which can be performed laparo- scopically. Small mucosal tumours of the stomach and duodenum can be managed with endoscopic resec- tion. Distal pancreatic tumours or pan- creatocutaneous fistulae are appro- priate for pancreatic tumours. Small-bowel resection along with resection of the draining lymph nodes is appropriate for carcinoid tumours. Standard colocolctal resec- tions are appropriate for colonic tumours. However, small peduncu- lated tumours are occasionally removed endoscopically.

Surgery in the setting of metastatic or unresectable disease

Small-bowel NETs (carcinoid tumours) present particular prob- lems related to the local effects of hormones produced by the tumour. This often results in a colonic response within the mesentry of the small bowel, producing ischaemic symptoms as well as obstruction. Simple bypass of the obstruction will not resolve the ischaemic symptoms, so resection of the associated lymphadenopha- thy within the mesentry is required. Even in the setting of unresectable metastatic disease, pal- liative resection of carcinoid tumours is still possible if warranted for control of the ischaemic and obstructive symptoms.

For patients with carcinoid syn- drome secondary to hepatic metastatic disease, surgical cure is still possible if complete resection of hepatic metastatic deposits can be performed. For patients in whom not all of the liver disease is resectable, symptom control is still possible if 90% of the disease can be removed or ablated. In both surgical situations (with curative or palliative intent), resection with or without ablative techniques (eg, microwave or radiofrequency ablation) can be used. For patients with extensive hepatic replacement by tumour, surgical resection is not possible. Hepatic transplantation has been used in this context but Australian guidelines do not recommend its use.

For locally advanced pancreatic tumours or pancreatic tumours with unresectable metastatic disease, there is little evidence to support the benefit of debulking surgery. If pres- ent, jaundice or castelio gastric outlet obstruction can be controlled with endoscopic techniques without the need for open surgery. In contrast to pancreatic adenocarcinomas, the obstructive symptoms are less fre- quent and worsen more slowly.

Anoathetic considerations

Preoperative anaesthetic prepara- tion is an important part of surgical managemen. Historically the mor- tality following resection of carci- nod tumours has been as high as 30%. This is due to the haemody- namic consequences of hormone release, as well as the presence of carcinoid heart disease. Cardiac echocardiography is required for patients with a raised CgA or symptoms of carcinoid heart dis- ease. Preoperative blockade with long-acting somatostatin analogues (described below) is beneficial and should be co-ordinated with anaes- thetic review.

Medical

The aim of medical therapy for patients with advanced NETs is to relieve symptoms related to the tumour (ie, hormone secre- tion or directly related to the pri- mary tumour or its metastases) and to slow down tumour growth. There is a broad range of medical treatments available, as outlined below.

Somatostatin analogues (SSAs) are indicated in patients with low- to intermediate-grade NETs whose disease is (weakly) positive on SSTR imaging and whose dis- ease is progressing on regular radiological review, whether they have functional or non-functional tumours.

SSA therapy is associated with 40–70% biochemical response, that is, a reduction in serum CgA and urinary 5-HIAA. Up to 70% of patients experience resolution of symptoms related to their car- cinoid syndrome, including diar- rhoea and flushing. There is some evidence that the response rates are higher with doses higher of the SSAs.

Apart from the inhibitory effects of somatostatin secre- tion, these agents also have an antiproliferative effect in slowing tumour growth, stabilising them radiologically in about two-thirds of patients, and inducing tumour regression in up to 10% of patients.1 The introduction of SSAs may be responsible for the increased survival of patients with NETs observed over the last two decades.

These agents do have adverse effects including:

• Nausea.
• Cramping.
• Diarrhoea.
• Steatorrhoea.
• Cardiac conduction abnormalities.
• Endocrine dysfunction (hypo-
thiroidism), hypothyroidism, and hyperthyroidism.

- Cholelithiasis in up to 50% of patients (although cholelithiasis develops in fewer than 5%). Patients undergoing surgical resection of NETs should be considered for prophylactic cholecystectomy to facilitate later use of SSAs.

There is still debate on the utility of SSAs in patients with somatostatin receptor-expressing but non-functional tumours whose disease is radiologically stable over a prolonged period of time. One option is continued observation; the other is to start SSA therapy for its antiproliferative effects. However, patients must be fully aware of their adverse effects and the need for prolonged therapy.

Symptomatic therapy

As stated above, SSAs are generally successful in controlling typical carcinoid syndrome symptoms such as diarrhoea and flushing. In some patients additional control can be achieved with use of over-the-counter antidiarrhoeal agents such as loperamide and/or cholestyramine. The latter may be particularly helpful in patients who have undergone an ideal or extensive small-bowel resection to counteract defective bile acid reabsorption.

Histamine oversecretion in gastric and thoracic NETs can induce skin rashers that can be treated with antihistamine type-1 blockers. Bromocriptine can be used with the usual antihistaminic preparations.

Management of cardiac failure secondary to carcinoid cardiac disease requires input by a cardiologist and an assessment of the need of valvular surgery.

Direct treatment of islet cell hormone secretion

Insulomas can cause episodic and often symptomatic hypoglycaemia. Sulfonylureas are the treatment of choice. Glucose lowering by modulating the carbohydrate stores or SSAs. Gastrinomas can be associated with Zollinger-Ellison syndrome, with severe peptic ulceration, and can be controlled with aggressive PPI therapy.

Chemotherapy

In the case of well-differentiated NETs, chemotherapy may be indicated when a patient’s disease has progressed despite SSA therapy, although increasingly radionuclide therapy is used in these patients, as discussed below. In general, classic carcinoid and islet cell tumours are poorly responsive to chemotherapy agents that are based upon streptozocin or doxorubicin. In contrast, somatostatin receptor-positive tumours may respond to more experimental agents such as streptozocin or doxorubicin.

Liver-directed therapies

The liver receives its blood supply mainly from the portal vein but also the hepatic artery. Liver metastases, however, receive their blood supply principally from the hepatic artery. Trans-arterial chemoembolisation (TACE) involves injecting slow-release chemotherapy-eluting beads into the hepatic artery via a catheter placed in the groin, with the aim of maximising the dose of chemotherapy to the metastases while minimising systemic side effects.

Another form of liver-directed therapy is intra-arterial administration of TACE-Spheres, which are microspheres impregnated with ytrium-90 (Y-90), a beta-radiation-emitting isotope. These treatments can have significant morbidity and should only be administered in specialist centres after careful consideration of risks vs benefits.

Bispecific therapies

These include the immunomodulator, alpha interferon, and the tyrosine kinase inhibitor, sunitinib (Sutent), and the m-TOR inhibitor, everolimus (Afinitor). These can be considered for the treatment of patients with low- to intermediate-grade pancreatic NETs who progress after prior therapies. All these agents can be associated with significant toxicity and so require careful monitoring by experienced oncologists. Quality-of-life considerations are important in the decision to use these agents and they are generally only indicated in patients with significant disease progression or uncontrolled symptoms.

Alpha interferon is a cytokine that increases the expression of the somatostatin receptors in NET cells and, therefore, has been used in combination with SSAs in patients in whom there is disease progression on SSA monotherapy. The combination is associated with a 40% biochemical and 10% radiological response rate.

Sunitinib (Sutent) is a tyrosine kinase inhibitor that acts on several pathways involved in the growth and spread of NETs. A recent randomised study has shown that sunitinib provides greater prolongation of tumour control and radiological response compared with placebo.$^{4}$

Everolimus (Afinitor). This is an oral drug that inhibits m-TOR, a protein that plays a central role in the growth of NET cells. Two recent randomised trials have demonstrated that everolimus combined with octreotide LAR (long-acting repeatable) provides greater prolongation of tumour control and radiological response compared with octreotide LAR alone.$^{5}$

Radionuclide therapy

Radionuclide therapy relies on the specific uptake and retention of a radioactive chemical within cancer cells, then the release of radiation that induces DNA damage in that cell or nearby cells. For almost 60 years radionuclide therapy has been used in the treatment of differentiated thyroid cancer. This situation the ability of thyroid cells to take up iodine, used in the synthesis of thyroid hormone, is leveraged to concentrate iodine-131 (I-131) within the tumour. The radioactive decay of this radioisotope leads to the emission of beta particles, which deposit all their energy in a single-cell diameter. While having a low toxicity profile, the low energy of the electron emitted limits the effectiveness of this therapy, especially in patients with a large disease burden.

The use of beta particle emitters Y-90 and lutetium-177 (Lu-177) in the form of Y-90 and Lu-177 DOTATATE (LuTate) are now preferred and have demonstrated excellent objective response rates (about 70%) with low toxicity. High-energy beta particles from Y-90 can travel up to a centimetre in tissue whereas lower-energy particles from Lu-177 travel 1-2 mm. Both result in ‘crossfire’, whereby each cell irradiates its neighbours, resulting in efficient radiation delivery to aggregates of cancer cells. These agents are generally administered as a series of 2-3 cycles at 6-12-weekly intervals. Subsequent consolidation or maintenance therapies are feasible in responders (figure 6, page 40). There is accumulating evidence that the effectiveness of these agents is enhanced by combining them with low-dose chemotherapy, which inhibits DNA repair, thereby sensitising cells to radiation damage, without significantly increasing toxicity. Due to its lower toxicity to the kidneys, LuTate is the preferred agent in most patients and has been administered to more than 200 patients in Australia since it was first trialled in 2001.

References


Online resources

- Unicorn Foundation (Australian charity focused on NETs): www.unicornfoundation.org.au
How to Treat Neuroendocrine tumours

— 16 March 2012

1. Which TWO statements are correct?
a) Neuroendocrine tumours (NETs) can occur at any gastrointestinal site from the stomach to the rectum
b) Pancreatic NETs arise from the exocrine cells of the pancreas
c) The term ‘carcinoid’ describes GI NETs that have rapid growth
d) Well-differentiated NETs tend to have slow growth with an indolent natural history

2. Which TWO statements are correct?
a) Well-differentiated NETs always secrete high and inappropriate levels of hormones
b) Serotonin is the hormone most commonly produced by carcinoid tumours
c) Well-differentiated NETs rarely express somatostatin receptors (SSTR) on their cell surface
d) Poorly differentiated NETs behave aggressively, with rapid cell proliferation and clinical course

3. Which TWO statements are correct?
a) Locally advanced or metastatic well-differentiated NETs are usually associated with significant symptoms
b) NETs that secrete serotonin are usually symptomatic well before they become metastatic

c) Characteristic symptoms of carcinoid syndrome include flushing, diarrhoea, abdominal cramps and wheezing
d) Chronic exposure to serotonin causes fibrosis and thickening of the tricuspid and pulmonary valves

4. Which THREE statements are correct?
a) Local secretion of serotonin can cause fibrosis leading to bowel obstruction, bowel ischaemia and malabsorption
b) Pancreatic NETs can cause diarrhoea as a result of pancreatic enzyme deficiency
c) Cushing’s syndrome, hypercaemia and hypertension can all be associated with functioning pancreatic NETs

d) Widespread metastatic NETs are usually aggressive and fast growing

5. Which TWO statements are correct?
a) Chromogranin-A (Cg-A) is a useful blood test for suspected NETs
b) Cg-A is only elevated in hormone-secreting NETs

c) Patients taking proton-pump inhibitors may have mild or moderate elevation in Cg-A levels

6. Which TWO statements are correct?
a) CT is highly sensitive for detecting the primary NET mass and the presence of metastases
b) Radionuclide somatostatin analogues are useful for imaging most NETs

7. Which TWO statements are correct?
a) High uptake of Octreoscan indicates that the NET is likely to have a rapid and aggressive natural history
b) Poorly differentiated NETs are metabolically very active and are identified by fluoro-deoxyglucose-PET scanning

c) The presence of metastatic disease means that curative or palliative surgery is not appropriate
d) Surgery for NETs can be combined with ablating techniques such as those using microwave or radio-frequency radiation

8. Which TWO statements are correct?
a) Preoperative use of long-acting somatostatin analogues (SSAs) decreases the risks of NETs by reducing the secretary function of the tumour
b) SSAs are only used in patients with functioning (ie, secreting) NETs

c) SSA therapy reduces the symptoms of carcinoid syndrome

9. Which THREE statements are correct?
a) SSAs may cause GI side effects, cardiovascular and respiratory abnormalities, and cholelithiasis
b) Norepinephrine or clonidine can be used in combination with SSAs for control of diarrhoea

10. Which THREE statements are correct?
a) Treatment can be targeted against liver metastases by injecting chemotherapy-eluting beads into the hepatic artery
b) Radionuclide therapy uses the specific uptake of a radioactive chemo into cancer cells, the radiation emitted damaging DNA in these cells or in nearby cells

Next Week: The next How To Treat looks at knee disorders in adults, ranging from traumatic and sporting injuries mostly in younger adults, to degenerative conditions in older patients. The author is Associate Professor Peter Papaniarchou, orthopaedic and lumbar spine surgeon, St George Private Hospital, Kogarah; St Luke’s Private Hospital, Elizabeth Bay; Dalcross Adventist Hospital, Killarney; and associate professor, Sydney Adventist Hospital Clinical School, University of Sydney.

Key points — management and prognosis

• Symptoms and disease biology are the most important determinants of both prognostic and treatment.
• Surgery should be considered as a curative option in patients with limited disease extent and can also provide palliative benefit even when all disease cannot be resected.
• Chemotherapy is generally ineffective in patients with well-differentiated NETs but may provide benefit in poorly differentiated disease.
• New biological therapies show promise for delaying disease progression in some patients.
• Liver-directed therapies are an option in selected patients but because of significant morbidity, these need to be performed in centres with expertise in NET management.
• Peptide receptor radionuclide therapy (PRRT) is a very effective and well-tolerated treatment in selected patients but availability is currently limited.

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