Chapter 7: Functional neuroendocrine neoplasms

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Practice Points

- Somatostatin analogues (SSAs) should be used in the treatment of patients with symptomatic carcinoid syndrome and as first-line therapy for the treatment of non-functional gastroenteropancreatic neuroendocrine neoplasms (GEP NENs) grade 1 and 2 in adult patients with unresectable locally advanced or metastatic disease.
- SSAs should be used for prevention and/or treatment of carcinoid crisis as part of the perioperative management of patients with GEP NENs[12]. It can also be considered when commencing peptide receptor radionuclide therapy, and occasionally prior to systemic chemotherapy if the functional symptoms are extreme.
- Patients with functional NENs should be screened every 6-12 months for carcinoid heart disease (including annual echocardiogram).
- Valvular abnormalities from carcinoid heart disease detected on echocardiogram should prompt an early cardiology referral, even if asymptomatic.

Background

Somatostatin is a cyclic peptide hormone that is found in the central nervous system, pancreas and gastro-intestinal tract. It has two isoforms, containing 14 and 28 amino acids. The former is more abundant. Somatostatin has a wide range of inhibitory functions, including inhibiting hypothalamic hormones, regulating gastrin and gastric acid secretion, and regulating the release of a number of other hormones including insulin, glucagon, pancreatic amylase, cholecystokinin, vaso-active intestinal peptide and secretin. It has also been shown to have anti-proliferative effects.[a]

Somatostatin receptors are expressed on the majority of neuroendocrine neoplasms (NENs). The naturally occurring somatostatin only has a very short half-life of 3 minutes, which limits its pharmacological use. The somatostatin analogues, octreotide and lanreotide, with longer half-lives, bind to somatostatin receptors on tumour cells and inhibit the release of serotonin in addition to other vaso-active substances.

The role of SSAs in improving the symptoms of the carcinoid syndrome from functional GEP NENs is well established and octreotide LAR and lanreotide have been a standard of care for some years in

Australia and New Zealand. Prevention of the development of carcinoid syndrome related fibrotic disease and carcinoid heart disease is also thought to be secondary benefits of controlling prolonged exposure to serotonin. It may be useful to initially commence patients on a short acting SSA if there are concerns regarding toxicity or an insulinoma (to assess treatment tolerability) before converting to a long acting preparation. Finally, a benefit from SSA therapy may be predicted by somatostatin scintigraphy (Gallium-68 dotatate PET scan), although there is relatively scant data regarding the exact SUV cut-offs to definitively inform clinical practice.

A common practice based on anecdotal/small series experience is to escalate the SSA dose or increase the frequency of administration of the long-acting agents as this may overcome primary or secondary treatment resistance, more often used as a bridging procedure prior to PRRT. However clinicians should be aware that some dosing regimens may not be fully reimbursed by the PBS.

Short acting SSAs should be used for prevention and/or treatment of carcinoid crisis as part of the perioperative management of patients with GEP NENs[12]. Prophylactic cover with SSAs is preferred in patients considered at risk of carcinoid crisis undergoing surgery and should be considered when commencing peptide receptor radionuclide therapy. Occasional indications also exist for use of SSAs pre systemic chemotherapy if the functional symptoms are extreme. Short acting octreotide is still used for breakthrough functional symptoms and around the time of surgical intervention or PRRT, given either as intermittent subcutaneous doses or via intravenous infusion.

The anti-proliferative activity of SSAs has been shown in randomized trials with both octreotide and lanreotide. The details of the PROMID and CLARINET studies are covered in Chapter 8: Systemic therapies: Somatostatin analogues and targeted agents.

A common question arising in clinical practice is the interplay between timing of long acting SSAs and 68Ga-DOTATATE PET. While the early Guidelines[b] recommend withholding long acting SSA therapy for at least 4 weeks prior to somatostatin receptor scintigraphy, the scan can be performed sooner as long as the interpreter is aware of the potential altered biodistribution, commonly a decrease in physiological uptake in the thyroid, liver and spleen and potentially an increase in tumour uptake[c,d]. The more recent EANM Guidelines[e] state that “There is no clear evidence that discontinuation of somatostatin analogues prior to PET imaging with 68Ga-DOTA-conjugated peptides is necessary”. Patients who are intolerant of an interruption of SSA therapy may be managed with short acting agents, which can be ceased close to the time of the scan.

Functional Syndrome (Carcinoid Syndrome)

Link to Chapter 12: Supportive Care Diet and Nutrition (p.6 "Diarrhoea management and diet").

Carcinoid syndrome is a term that describes the constellation of symptoms related to various hormones secreted by some NENs [7]. Most common symptoms include flushing, diarrhoea and bronchoconstriction. The majority of patients with carcinoid syndrome have metastatic disease typically to the liver which secretes hormones directly into the systemic circulation. The most important hormone implicated in causing these symptoms, especially diarrhoea is serotonin. The enzyme tryptophan hydroxylase is an important rate limiting step in the conversion of the amino acid tryptophan to serotonin.

Standard SSA is first line therapy as noted for functional syndromes. An oral tryptophan hydroxylase inhibitor (Telotristat ethyl) was developed to help control diarrhoea associated with carcinoid syndrome in conjunction with SSA therapy for patients failing standard therapy. The FDA approval in 2017 was based on the results of the TELESTAR Trial[8] where treatment with telotristat was associated with a statistically significant reduction in the frequency of bowel movement over time compared to placebo. Telotristat was approved by the TGA in September 2018 but is not as yet subsidized by the PBS in Australia.

Carcinoid Crisis

Carcinoid crisis is a life threatening form of carcinoid syndrome which typically presents as wide blood pressure fluctuations with a predominance of hypotension. This is secondary to the release of large amounts of biologically active substances that could be the results of tumour manipulation (biopsy or during surgery) or by anaesthesia. Increasingly it is also seen as a result of PRRT or liver directed therapies. Symptoms are generally resistant to fluid resuscitation alone[9,10,11]. Management of hypotension can be with an octreotide infusion (500 to 1000 mcg intravenously; a continuous intravenous drip of octreotide at a rate of 50 to 200 mcg/hour may also be used). [9,12]

Carcinoid Heart Disease

Carcinoid heart disease occurs in 20-50% of patients with carcinoid syndrome[13,14]. Chronic exposure to high concentration of circulating serotonin is thought to be a major factor in the development of carcinoid heart disease. Usually it is characterized by plaque like fibrous endocardial thickening that involves the right side of the heart and often leads to retraction and fixation of the leaflets of the tricuspid and pulmonary valves. Symptoms usually include fatigue and dyspnoea on exertion which

can progress to right side heart failure with worsening dysponea, oedema and ascites. Tricuspid regurgitation is the most common finding on echocardiogram. Patients with carcinoid syndrome planning to undergo liver or abdominal surgery should be screened for carcinoid heart disease due to the risk of haemorrhage with elevated right heart pressures[15].

Patients with carcinoid syndrome should undergo 6 to 12 monthly clinical evaluation for symptoms and signs of heart failure. Elevated levels of 5-HIAA, especially a 24 hour urine collection > 300 umol/24hr, is a useful marker for identifying those at risk of developing carcinoid heart disease. Measurement is recommended in patients with small intestinal NENs, including those with non-functioning tumours because few patients may display high 5-HIAA levels in the absence of a clinical syndrome[16]. NT-Pro BNP is the best marker to date for screening patients with carcinoid syndrome for evidence of clinically significant heart disease with a cut-off level of 260 pg/ml[16].

Echocardiogram remains the gold standard tool for diagnosis and follow up of carcinoid heart disease and should be considered every 12 months when functional syndrome or elevated 5-HIAA is present[16]. Early referral to a Cardiology team (cardiologist and cardiothoracic surgeon) with experience of carcinoid heart disease should be considered if changes are seen on echocardiogram.

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