New Treatments for the Carcinoid Syndrome

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KEYWORDS

• Everolimus • Medical treatment • Surgery • Peptide receptor radionuclide therapy • Somatostatin receptor ligands • Sunitinib • Telotristat etiprate • Theranostics

KEY POINTS

- There is consensus that an individualized patient pathway agreed to by a multidisciplinary team is the optimal planning approach to treatment.
- Use of somatostatin receptor ligands as first-line therapy has been the paradigm for some time but this may now be challenged with newer trial data on mammalian target of rapamycin inhibitor and after peptide receptor radionuclide therapy (PRRT).
- It is anticipated that as PRRT becomes more widely available it may become second-line or first-line therapy.

BACKGROUND

The first multiple distal ileal neuroendocrine tumors (NETs) were found at autopsy in 1888 by Lubarsch and the name karzinoide or carcinoma-like tumor was later coined by Oberndorfer in 1907.[1–3] Carcinoid tumors are derived from enterochromaffin or Kulchitsky cells.[4,5] A variety of biochemical syndromes are associated with carcinoid tumors with foregut tumors (lungs, thymus, duodenum, and pancreas), which cause angioedema, a hive-like pink flushing or rash due to histamine, 5-hydroxytryptophan (5-HTP), and other vasoactive substances, and with serotonin-secreting midgut tumors (small intestine, appendix, and proximal colon),[6,7] which is the cause the classic carcinoid syndrome (CS) with nondiaphoretic flushing, diarrhea, and occasional wheezing due to right-sided cardiac failure following cardiac valve stenosis or

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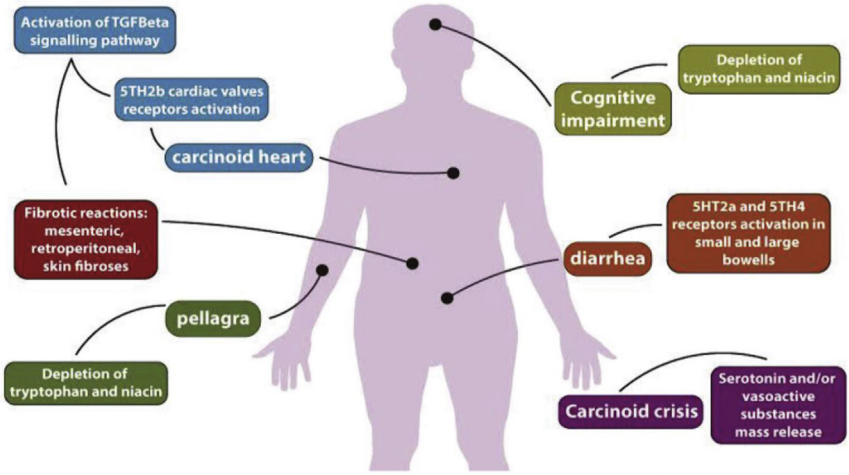
thickening[5] (Fig. 1). Hindgut tumors (transverse colon, sigmoid colon, and rectum) infrequently secrete hormones and typically are either incidentally discovered on lower gastrointestinal (GI) endoscopy or present with obstructive symptoms.



Symptoms	Frequency	Mediators	Treatment
Profound Flushing	85%–90%	Kallikrein, histamine, 5-hydroxtryptamine, prostaglandins, substance P	Somatostatin receptor ligands, Octreotide; H1 and H2 blockers, Prednisolone
Diarrhea	70%	Gastrin, histamine, 5-hydroxtryptamine, prostaglandins, vasoactive intestinal peptide	Loperamide, Diphenoxylate, Methysergide,
Abdominal Pain	35%	Small bowel obstruction due to tumor or tumor products, mesenteric ischemia, hepatomegaly	Oxycodone
Bronchospasm	15%	Histamine, 5-hydroxtryptamine,	Aminophylline
Pellagra	5%	Niacin deficiency	
Hypotension	30%	5-hydroxtryptamine, substance P	Methoxamine, Norepinephrine
Teleangiectasis	25%	N/A	

Fig. 1. Main features of midgut CS and carcinoid crisis, with treatment options. CS is usually caused by primary well-differentiated midgut NET with hepatic metastatic lesions that release vasoactive compounds. Carcinoid crisis is characterized by profound flushing, bronchospasm, tachycardia, and hypotension, and is usually precipitated by tumor cytoreductive surgery, embolization, or radio ablation. Serotonin antagonists and somatostatin receptor ligands are the major treatment options. TGF, transforming growth factor; 5HT2a, serotonin receptor 2a; 5TH2b, serotonin receptor 2b; 5TH4, serotonin receptor 4. (*Adapted from* Mota JM, Sousa LG, Riechelmann RP. Complications from carcinoid syndrome: review of the current evidence. Ecancermedicalscience 2016;10:662; with permission.)