Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo

www.spedmjournal.com

Artigo Revisão

Carcinoid Syndrome: A Review

Diana Borges Duarte [a,*], Raquel G. Martins [b]

[a] Serviço de Endocrinologia, Diabetes e Metabolismo, Centro Hospitalar e Universitário do Porto, Porto, Portugal
[b] Serviço de Endocrinologia, Instituto Português de Oncologia de Coimbra, Coimbra, Portugal

INFORMAÇÃO SOBRE O ARTIGO

Historial do artigo:
Received/ Recebido: 2022-06-30
Accepted/Aceite: 2022-08-18
Publicado / Published: 2023-01-18

Keywords:
Malignant Carcinoid Syndrome/diagnosis;
Malignant Carcinoid Syndrome/drug therapy;
Malignant Carcinoid Syndrome/physiopathology;
Neuroendocrine Tumors/complications.

A B S T R A C T

Carcinoid syndrome (CS) is a debilitating disease caused by the production of a variety of biologically active substances by functional neuroendocrine neoplasms (NENs). While the reported frequency of CS among NEN patients has been inconsistent, the negative impact on patient quality of life is clearly established.
The cardinal presenting features of CS are flushing, diarrhoea, abdominal pain and valvular heart disease; other signs and symptoms can include wheezing, telangiectasias, pellagra, and the complications of mesenteric fibrosis, including bowel obstruction and ischemia. These symptoms are mediated by the release of serotonin, histamine, kallikrein, prostaglandins and tachykinins.
There have been advances in many aspects of the carcinoid-syndrome all of which are reviewed in this article, including new methods to establish diagnosis, an increased understanding of natural history and pathogenesis and important new approaches to its treatment.

Palavras-chave:
Síndrome do Carcinoide Maligno/diangóstico;
Síndrome do Carcinoide Maligno/fisiopatologia;
Síndrome do Carcinoide Maligno/tratamento farmacológico;
Tumores Neuroendócrinos/complicações.

Síndrome Carcinóide: Revisão

R E S U M O

A síndrome carcinóide (SC) é uma doença debilitante causada pela produção de múltiplas substâncias biológicas ativas por neoplasias neuroendócrinas (NENs). Apesar da variabilidade na frequência reportada, o impacto negativo na qualidade de vida dos pacientes com NENs está bem estabelecido.
A apresentação clássica da SC inclui o *flushing*, a diarreia, a dor abdominal e a doença valvular cardíaca; outros sinais e sintomas incluem o broncoespasmo, telangiectasias, pelagra e as complicações da fibrose mesentérica como obstrução e isquemia intestinal. Estes sintomas são mediados pela libertação de serotonina, histamina, calicreína, prostaglandinas e taquicininas.
A síndrome carcinóide tem sido alvo de vários avanços, incluindo novos métodos de diagnóstico, um aperfeiçoamento na compreensão da sua história natural e patogénese, e novas abordagens terapêuticas, que serão abordados neste artigo.

* Autor Correspondente / Corresponding Author.
E-Mail: diana.sbduarte@gmail.com (Diana Borges Duarte)
Centro Hospitalar e Universitário do Porto, Largo Prof. Abel Salazar
4099-001 Porto, Portugal

https://doi.org/10.26497/ar220042

1. Introduction

Carcinoid syndrome (CS) is a debilitating disease caused by the production of a variety of biologically active substances by functional neuroendocrine neoplasms (NEN).[1] The classical example of a hormonal syndrome, CS was first described in 1931.[2] Recently, the frequency of CS was assessed in a Surveillance, Epidemiology, and End Results (SEER) database in the USA; the authors have reported an increasing incidence of carcinoid syndrome between 2000 and 2011 and, among the 9512 patients diagnosed with NEN over this period, symptoms of CS were reported in 18.8%.[3] While the reported frequency of CS among NEN patients has been inconsistent, the negative impact on patient quality of life(QoL) is clearly established.[4–6]

2. Pathophysiology

Neuroendocrine neoplasms may secrete numerous active substances that are potential mediators of the clinical features of CS; the most prominent being 5-hydroxytryptamine (5-HT, serotonin), commonly used to assess for the presence of CS by determining the serotonin-metabolite, 5-hydroxy-indole acetic acid (5-HIAA), in the urine.[7] Due to the absence of the aromatic amino acid decarboxylase, that converts 5-hydroxytryptophan (5-HTP) to 5-HT, foregut NEN secrete 5-HTP instead of 5-HT (see atypical carcinoid syndrome).[7] Other co-secreted peptide hormones and amines include tachykinins (substance P and neurokinin A), bradykinins, histamine and prostaglandins.[7]

Serotonin is considered the main mediator of diarrhoea in CS, due to its effects on gut motility and secretion,[8–11] and a main driver of fibrotic complications such as retroperitoneal, mesenteric and cardiac valvular fibrosis in carcinoid heart disease.[10–14] On the other hand, bronchial constriction is predominantly mediated by tachykinins and bradykinins that cause constriction of smooth muscle in the respiratory tract and local oedema in the airways.[10,15] Although the cutaneous flushing pathophysiology is not well established yet, several vasodilators, such as tachykinins, bradykinins, prostaglandins, and histamine are thought to be involved.[10,15,16]

Carcinoid syndrome occurs when sufficient amount of tumour-released bioactive products reaches the systemic circulation, escaping the first pass inactivation in the liver.[1,10] Carcinoid syndrome is thus predominantly encountered in patients with midgut NENs with liver metastases, in which these bioactive products escape inactivation in the liver.[10] Ovarian NENs and large retroperitoneal metastases from midgut NENs are associated with CS in the absence of liver metastases as bioactive amines are released directly into the systemic circulation, bypassing hepatic inactivation.[10] The inactivation of the bioactive tumour products also occurs in the pulmonary circulation; the predominance of right-sided plaque-like thickenings of endocardium, valves, atria and ventricles in carcinoid heart disease supports this mechanism and differential exposure.[7,10,12] The exception, with both left and right-sided heart-valves involvement, is seen in bronchial NENs or in right-to-left shunt.[7,10,12]

3. Clinical features

The cardinal presenting features of the CS are flushing, secretory diarrhoea, abdominal pain and valvular heart disease[14]; nevertheless, a typical patient with CS may also present with telangiectasia, valvular heart disease, intermittent bronchial wheezing, and pellagra.[7,17]

3.1 Flushing

Flushing is a subjective sensation of warmth that is accompanied by reddening of the skin anywhere on the body but favours the face, neck, and upper torso.[18] Flushing in CS may occur spontaneously or be triggered by stress (physical and emotional), alcohol, drugs (pentagastrin, catecholamines, dopamine, isoproterenol), exercise or tyramine-containing-foods like chocolate, bananas, cheese, red wine or walnuts.[14,16,19] Four types of flushing are distinguished: erythematous, violaceous, prolonged and bright red.[19]

The first type is the sudden, short-lived (1 to 5 minutes) and diffuse erythematous flush, usually affecting the face, neck, and upper chest; it is associated to early-stage midgut NENs.[14,17]

The second type is the violaceous flush; it affects the same area of the body and has approximately the same time course as the erythematous flush. Additionally, patients may also have facial telangiectasias and may not report the flushing as they have become accustomed.[19] This kind of flush occurs during the later stages of midgut NENs.[19]

The third type is prolonged flushing, lasting from a couple of hours to several days; it may involve the whole body and it is sometimes associated with profuse lacrimation, swelling of the salivary gland, hypotension, and facial oedema; this type of flushing is usually associated with malignant bronchial NENs and is thought to be 5-HTP and/or histamine-induced.[17,19]

The fourth type is a bright red, patchy flush seen in patients with chronic atrophic gastritis and gastric enterochromaffin cell hyperplasia; these symptoms are associated with an increased release of histamine.[17,19]

The differential diagnosis of flushing includes both physiologic (such as menopause) and pathologic causes from non-neuroendocrine disorders (POEMS syndrome, central hypogonadism, orthostatic hypotension, panic attacks) to other neuroendocrine entities (medullary thyroid carcinoma, pheochromocytoma and paraganglioma, endogenous Cushing's syndrome).[16,19]

3.2 Diarrhoea

The diarrhoea is typically secretory and intermittent, often associated with abdominal cramping which may result from mesenteric fibrosis.[17,19] Malabsorption features can develop from intestinal resections, lymphangiectasia, secondary to mesenteric fibrosis, from bacterial overgrowth, intestinal blockage by the primary tumour or rapid intestinal transit. Additionally, increased secretion by the small bowel associated with accelerated transit can overwhelm the normal storage and absorptive capacity of proximal colon.[17,19]

In a study of patients with CS, transit time in the small bowel and colon was significantly decreased when compared to normal subjects; the volume of the ascending colon was smaller, and the postprandial colonic tone increased.[20] Overall, although initially a secretory one, diarrhoea can develop malabsorption features and associate alterations in gut motor function.[19,20] Nevertheless, determining the underlying cause of diarrhoea can be challenging as patients with NENs may experience uncontrolled diarrhoea due to surgical complications or treatment with somatostatin analogues; pancreatic exocrine insufficiency, inflammatory bowel disease, irritable bowel syndrome, lactose intolerance or celiac disease are other etiologies to consider.[21]

3.3 Carcinoid heart disease (Hedinger's syndrome)

Carcinoid heart disease (CHD) is a severe complication of CS characterized by the development of plaque-like fibrous endocardial

thickening that affects primarily the right-sided valves.[12,17,19] It is associated with increased morbidity and mortality, leading to progressive dysfunction of the cardiac valves and ultimately to congestive heart failure.[12] Echocardiography can demonstrate lesions in about 60%-80% of CS patients although it is clinically significant in a much smaller percentage.[12,17,19] Prevalence of CHD has decreased to approximately 20%, probably due to earlier CS diagnosis and initiation of antitumour treatment such as somatostatin analogues.[12,17,19,,22]

There is often an asymptomatic period; in symptomatic patients, dyspnoea and fatigue are the most encountered symptoms.[12] Patients with ≥3 episodes of flushing per day and those who have significantly higher levels of urinary 5-HIAA (see diagnosis) are at increased risk of developing CHD; this latter biomarker has been shown to be an independent predictor for the development and progression of CHD.[12,17,19,22–24]

3.4 Other clinical features

Bronchial constriction with wheezing may be present, particularly during a carcinoid crisis.[17,19] Fibrotic complications other than CHD may occur, such as intra-abdominal fibrosis (that can lead to intestinal adhesions and bowel obstruction), retroperitoneal fibrosis (that may result in obstruction of the ureter with kidney function impairment), occlusion of the mesenteric arteries and veins, Peyronie's disease and carcinoid arthropathy.[17,19] Other rare features of CS result from diversion of dietary tryptophan for synthesis of serotonin which may develop pellagra (skin rashes, glossitis, stomatitis, dementia/mental confusion) and reduced protein synthesis with hypoalbuminemia and myopathy.[17,19]

3.5 Carcinoid crisis

Carcinoid crisis is a severe and potentially life-threatening exacerbation of hormonal symptoms of the CS, due to the release of large amounts of amines in the circulation.[17] Hypotension, rarely hypertension, tachycardia, arrhythmias, hyperthermia, bronchoconstriction, severe flushing and central nervous system dysfunction dominate the clinical presentation.[17,19,25] Carcinoid crisis can occur spontaneously or be precipitated by anaesthesia, infection, chemotherapy or interventional procedures (surgery, embolization procedures, peptide receptor radionuclide therapy).[17,19,25,26] Concerning anaesthesia, drugs that stimulate the sympathetic nervous system or cause histamine release, such as morphine and d-tubocurarine should be avoided; propofol has a more profound effect in supressing catecholamine release and may the best agent in patients with CS as long as hypotension is avoided.[25] Intravenous octreotide might be used in combination with volume expanders to correct hypotension; the latter can also have a role in the treatment of bronchospasm as β-receptor agonist and theophylline may precipitate mediator release; corticosteroids (dexamethasone) may also be used.[25]

The presence of a high tumour load, CHD, high urinary 5-HIAA values or high chromogranin A levels are risk factors for the development of carcinoid crisis.[25] Peri-operative carcinoid crisis prophylaxis with somatostatin analogues is advised (see treatment).[25]

3.6 Atypical carcinoid syndrome

An atypical carcinoid syndrome may be encountered in patients with tumours originating from the foregut including mostly the lung, but also the stomach and duodenum.[19,25] Patients with the atypical carcinoid syndrome have a decarboxylation deficit and therefore only seldom have excess urinary excretion of the serotonin metabolite 5-HIAA.[19,25] The syndrome consists of patchy, intensely red flush, sweating, itching, sometimes also cutaneous oedema, bronchoconstriction, salivary gland swelling, lacrimation, and cardiovascular instability mainly manifested as hypotension and it is due to the release of both histamine and serotonin.[19,25] Like typical carcinoid syndrome patients, in the presence of an atypical carcinoid syndrome, the patients should be treated with somatostatin analogues and a combination of histamine-1(H1) and histamine-2(H2) receptor blockers as prophylaxis treatment of carcinoid crisis before, during and after high-risk procedures.[25]

3.7 Refractory carcinoid syndrome

Refractory carcinoid syndrome (RCS) is defined by recurring or persisting CS symptoms and increasing or persistently high urinary 5-HIAA levels despite the use of maximum label doses of SSA.[27] RCS may be divided into either non-aggressive or aggressive, based on symptoms burden (<4 or ≥ bowel movements per day, and/or < or ≥ 5 flushing episodes per day, respectively) together with disease stability (stable or progressive), hepatic burden (< or ≥ 50% liver involvement) and/or the presence of carcinoid heart disease.[27]

4. Diagnosis

The presence of CS is considered when a patient has suggestive symptoms.[7,19] The most frequent initial diagnostic method is assessment of 5-HIAA levels.[7]

4.1 Biochemical diagnosis

The preferred initial diagnostic test for CS is to measure 24-hour urinary excretion of 5-HIAA; various foods and drugs (Table 1) can

Table 1. Factors that interfere with urinary 5-HIAA measurement [adapted from[19]]

Factors that produce false-positive results	
Foods	Drugs
Avocado	Acetaminophen
Banana	Acetanilide
Chocolate	Caffeine
Coffee	Fluorouracil
Eggplant	Guaifenesin
Pecan	L-Dopa
Pineapple	Melphalan
Plum	Mephenesin
Tea	Metamphetamine
Walnuts	Methocarbamol
	Methydergide maleate
	Phenmetrazine
	Reserpine
	Salicylates
Factors that produce false-negative results	
Foods	Drugs
None	Corticotropin
	p-Chlorophenylalanine
	Chlorpromazine
	Heparin
	Isoniazid
	Methenamine mandelate
	Methyldopa
	Monoamine oxidase inhibitors
	Phenothiazine
	Promethazine

interfere with the measurement and patients should avoid them for two to three days prior to urine collection.[7,19,28] Normal rate of urinary 5-HIAA excretion is <10 mg/day; elevated levels are usually found but foregut NENs tend to produce an atypical CS with normal or only slightly elevated 5-HIAA.[19] Measurement of 5-HIAA levels in all patients with small intestinal NENs is recommended because few patients may display high 5-HIAA levels in the absence of a clinical syndrome.[29]

Recently, a serum 5-HIAA measurement method has been developed with close correlation with urinary 5-HIAA; the absence of food interference and the ability to assess 5-HIAA levels with a single determination are the main advantages.[7,30,31]

4.2 Diagnosis of carcinoid heart disease

Transthoracic echocardiography is the gold-standard for the diagnosis and monitoring of carcinoid heart disease and several echocardiographic scoring systems were developed; cardiac magnetic resonance imaging (MRI) may have a complementary role in the diagnosis.[12,32] N-terminal pro-B type natriuretic peptide (NT-proBNP) is the most appropriate marker with both diagnostic and prognostic value for heart diseases; in patients with CS the cut-off value in CHD screening is 260 pg/mL((31 pmol/L).[32] Another useful marker in the assessment of CHD is 5-HIAA; a 24-hour urinary 5-HIAA >300 mmol/L helps identify subjects with increased risk of CHD development.[32]

5. Treatment

The treatment of choice for a patient who has a localized NEN is usually surgery with curative intent; systemic treatment options to control tumour growth and hormone hypersecretion and to improve patient's quality of life are used in metastatic NEN.[27]

5.1 Nutrition, lifestyle, and symptomatic treatment

Regular screening of nutritional status is required.[33] Tryptophan is the common precursor of serotonin and niacin (vitamin B3); in CS, as most niacin is metabolized to serotonin, niacin deficiency is common and can result in pellagra.[34] Supplementation with high-doses of niacin (50-500 mg/day) or niacin-enriched food may be required.[34] Additionally, deficiencies of fat-soluble vitamins, which may occasionally follow treatment with somatostatin analogues, should be sought and supplemented.[35]

For flushing, lifestyle adjustments include alcohol eviction as well as avoiding spicy foods and strenuous exercise.[33] Loperamide (doses up to 16 mg daily) can be used in refractory cases of diarrhoea.[33]

5.2 Pharmacologic treatment

Somatostatin analogues (SSAs)

Somatostatin is a peptide hormone that inhibits the secretion of a broad range of hormones by binding to somatostatin receptors which are expressed on the majority of NENs.[36] Somatostatin analogues targeting predominantly somatostatin receptor subtype 2, octreotide and lanreotide, are the standard initial treatment for CS for its anti-secretory and antiproliferative effects in NEN patients.[1] In a recent meta-analysis of studies with SSA in CS patients, octreotide induced a response of overall symptoms in 66%, of diarrhoea in 65% and of flushes in 72% of subjects; while lanreotide experienced similar responses rates of 65%, 65% and 69%, respectively.[1] Overall, control of the most relevant CS symptoms with doses of octreotide long acting-release (LAR) 20-30 mg or lanreotide autogel 90 to 120 mg every 4 weeks was obtained in 66%-70% of patients.[1] Biochemical response of 5-HIAA levels occurred in 45%-46% of CS patients.[1]

Despite the clear efficacy of SSAs, loss of response can occur after prolonged use. Downregulation of somatostatin receptors on tumour cell surface has been hypothesized to underlie tachyphylaxis.[1] Escalation of dose or frequency (to 21 days) of a SSA may be necessary for patients with refractory symptoms; these strategies result in a reduction of diarrhoea and flushes in 72% and 84% of the patients, respectively. However, 5-HIAA reduction was achieved in only 29%.[1] An alternative strategy, switching either octreotide or lanreotide to pasireotide, a SSA that targets somatostatin receptor subtypes 1-3 and 5, led to symptomatic response in 27% of patients.[37] However, a randomized phase III study of pasireotide LAR versus high-dose (40 mg) octreotide LAR in patients with advanced gastroenteropancreatic NENs failed to show superiority of pasireotide LAR in comparison with first-generation SSAs at maximum approved doses.[38] SSA treatment was associated with higher health-related quality of life (HR-QoL).[39,40]

Telotristat ethyl

Telotristat ethyl is a serotonin synthesis inhibitor, acting by inhibiting tryptophan hydroxylase, the rate-limiting enzyme in the production of serotonin from tryptophan.[10] On the TELESTAR trial, a three-arm study evaluating two doses of oral telotristat ethyl (250 and 500 mg, each taken three times daily) against placebo, conducted in patients with CS with uncontrolled diarrhoea (≥ 4 bowel movements daily) treated with SSA, the drug was associated with a significant reduction in bowel movement frequency and 5-HIAA levels.[41] Long-term improvement in HR-QoL was also reported.[42–44] The drug was well tolerated and is approved in combination with a SSA for the treatment of adults with CS-associated diarrhoea inadequately controlled with SSA monotherapy; the recommended dose is 250 mg three times daily.[41]

Interferon alpha

Interferon-α (IFN-α) exerts a direct effect on tumour cells by blocking cell division and reducing angiogenesis.[36] Additionally, IFN-α produces upregulation of somatostatin receptors, suggesting a synergistic effect.[45]

The recommended dose of INF-α is 3-9MU subcutaneously every other day; slow-release formulation is given subcutaneously once a week (80-100 mg).[46] In several single-arm prospective series, the reported response rates of INF monotherapy varied between 0%-90% and 50%-80% for clinical and biochemical control, respectively.[1] Patients with CS who have not responded to octreotide or IFN-α alone may be given a combination of both agents; such combinations have generated symptomatic control in 70% of patients and stabilization of tumour growth in 40% to 50% of patients.[19] Low tolerability of the drug due do its side effects (flu-like symptoms, chronic fatigue, liver and bone marrow toxicity, autoimmune reactions) limits its use to few experienced centers.[19]

Liver-directed therapies

Liver-directed therapies have been reported to be effective in controlling CS symptoms in SSAs resistant patients with disease limited to the liver; these include radiofrequency ablation, trans-

arterial chemoembolization/trans-arterial embolization, radioembolization or selective internal radiation therapy with 90y yttrium-labeled microspheres and hepatic-segment resection.[1]

Data on outcomes of liver-directed therapies is scarce; in most of the studies clinical response is described without further quantification, but overall reported clinical and biochemical response rates are high.[1] Most of the studies concerned treatments with embolization; when all embolization techniques were combined, response rates are 82% and 63% for overall symptoms and 5-HIAA levels, respectively.[1] The efficacy does not appear to be influenced by previous use of SSAs.[1]

Peptide receptor radionuclide therapy (PRRT)

The NETTER-1 study, conducted on patients with progressive metastatic midgut NENs to receive ^{177}Lu-DOTATE plus octreotide 30 mg LAR every four weeks vs high-dose octreotide (60 mg every four weeks), demonstrated improvement in clinically relevant symptoms such as diarrhoea and health-related quality of life with no significant change found on flushing.[47,49]

PRRT is usually well-tolerated with self-limiting acute side effects of nausea and vomiting; the potential exacerbation of hormonal syndromes leading to carcinoid crisis during/after PRRT although rare must be acknowledged.[49] The most serious long-term toxicity associated with PRRT is irreversible myelotoxicity and therapy-related myeloid neoplasms.[50]

Everolimus

A mechanistic target of rapamycin (mTOR) inhibitor, everolimus, proved its effectiveness in progression-free survival in non-functional lung or gastrointestinal NENs (RADIANT-4).[51] In another trial in patients with carcinoid syndrome (RADIANT-2), the combination of octreotide LAR 30 mg q28d with everolimus 10 mg daily was associated with a slight but significant improvement in 5-HIAA (61% *vs* 54% in octreotide LAR monotherapy), although no difference in the overall survival was noted and symptom control was not assessed.[52] Of note, everolimus side-effects, which include diarrhoea, may be challenging in CS patients.[52]

5.3 Treatment and prophylaxis of carcinoid crisis

Patients with CS are at risk of developing a carcinoid crisis during high-risk procedures (see above). Periprocedure prophylactic treatment of choice is intravenous octreotide at a starting dose of 50-100 µg/h with dose escalation until symptom control is obtained (mean dose of 100-200 µg/h).[25] Most experts initiate treatment at least 12 hours before the procedure and continue at least 48 hours after, as late-onset events have been described.[25] Patients pre-treated with SSAs may require even higher doses of intravenous octreotide.[25]

Patients with atypical carcinoid syndrome should be treated with prophylactic octreotide but may require higher doses (100-200 µg/h) and sometimes saline infusion. Combination treatment with H1 receptor blockers (loratadine), H2 blockers (ranitidine) and dexamethasone is recommended in severe cases to further block histamine release.[25]

Concerning anaesthesia, drugs that stimulate the sympathetic nervous symptoms or cause histamine release such as morphine and d-tubocurarine should be avoided; for anaesthesia induction, propofol may be the best agent as it has a more profound effect in supressing catecholamines release.[25] Only nondepolarizing neuromuscular blockers that do not cause histamine release should be used, vecuronium and rocuronium can be safely used. During maintenance of anaesthesia, attention should be paid to avoid right ventricular overload and strain to prevent right ventricular failure.[25] Hypotension is the most common problem during anaesthesia, and, in this case, sympathomimetic drugs should be avoided as they may worsen hypotension by triggering peptides release.[25] Hypotension tends to occur during manipulation of large bulky metastases; procedure should be stopped until hemodynamic control is restored and intravenous octreotide in association with volume expanders can be used.[25]

5.4 Treatment of carcinoid heart disease

The main challenge in CHD management rises from the necessity to simultaneously address the tumour burden (and 5-HT secretion), the CS symptoms, and the heart failure.

Antiproliferative and antisecretory therapy

Considering the crucial role of 5-HT in the cascade of events leading to the development of CHD, it is pivotal to control serotonin production from the tumour.[12]

Considering medical therapy, long-acting SSAs, octreotide and lanreotide (with association of telotristat ethyl if needed), have shown substantial reductions in serotonin production and antiproliferative effect (see above).[29]

Peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE is an effective antiproliferative therapy in progressive disease refractory to first line SSAs; a particular concern with this therapy is volume overload in patients with heart failure due to the nephroprotective amino acid infusion as part of the PRRT protocol.[29] A prolonged infusion might be considered[53]; a recent report of nine CHD patients treated with PRRT showed no acute cardiac complications in association with PRRT.[54] However, patients with uncontrolled congestive heart failure [New York Heart Association (NYHA) class II-IV were not eligible for treatment with ^{177}Lu-DOTATTE treatment in NETTER-1 study.[48] Current ENETS guidelines consider severe cardiac impairment (NYHA class III or IV) an absolute contraindication.[55]

Non-cardiac interventions

Transcatheter arterial embolization (TAE) is an efficient method in decreasing tumour burden and hormone levels in individuals with substantial metastases in the liver.[29] However, it must be used with caution in patients with severe CHD and right ventricular dysfunction and/or high hepatic tumour burden due to potential adverse effects such as bleeding or liver failure.[29] It is recommended that TAE should be exploited in the early disease stages before cardiac insufficiency occurs and should be used with caution (embolization procedures can be staged, and different liver segments may be embolized in repetitive small sessions) when carcinoid heart disease is present.[29] Complete portal vein occlusion, poor performance status and hepatic insufficiency are considered relative contraindications.[29]

Surgical hepatic debulking decreases CHD progression and improves prognosis[58]; similar to TAE, debulking surgery should be performed with caution and its recommended for patients with advanced valve disease after heart valve replacement.[29]

Pharmacotherapy for heart failure

Medical management consists of relieving symptoms of right-sided heart failure with a combination of loop and thiazide diuretic agents, as well as aldosterone antagonist therapy.[29] However, these measures should be used judiciously, as depletion of intravascular volume can further reduce cardiac output, leading to fatigue and breathlessness.[57] Other treatments, including digoxin, vasodilators, and angiotensin-converting enzyme inhibitors, can be considered, but they have no proven efficacy in this population.[29,57]

Heart valve replacement

Heart valve replacement is the most effective treatment option for advanced carcinoid heart disease.[58] The optimal timing of surgery in relation to the severity of valve dysfunction and symptoms has not been identified; a recommended indication for valve replacement is right ventricular dysfunction (symptomatic or evidence in echocardiography) with at least 12 months of anticipated post-operative survival from their NEN.[29] A trend towards earlier intervention, including patients with metastatic NENs prior to any primary-tumour debulking surgery or liver-directed therapies, has been observed.[59,60] The choice of valve prosthesis should be individually tailored based on the patient's bleeding risk and possible future therapeutic interventions. Biological valve prostheses are the preferred option.[29] Prophylactic treatment for carcinoid crisis must be implemented in the peri-procedure period.[29]

6. Conclusion

In the last years there have been many advances in the management of NENs and its functional syndromes such as the more frequent, carcinoid syndrome. There is a strengthened awareness of its pathogenesis, its epidemiology and increasing frequency; new methods to establish its diagnosis and new approaches to its treatment, namely for patients with carcinoid syndrome refractory to somatostatin analogues. Carcinoid heart disease, a significant cause of morbidity and mortality in patients with carcinoid syndrome, has seen new non-surgical therapeutic advances with the potential to prevent its development or to slow its progression which has significantly improved the prognosis of these individuals.

The presence of the endocrinologist in the multidisciplinary care team is essential for the management of these neoplasms, as many functioning tumours may be underdiagnosed in non-specialized centers.

Contributorship Statement / Declaração de Contribuição:

DBD: conceptualization, writing and review.
RGM: conceptualization, review.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram não possuir conflitos de interesse.
Suporte Financeiro: O presente trabalho não foi suportado por nenhum subsidio o bolsa ou bolsa.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financial Support: This work has not received any contribution grant or scholarship.
Provenance and Peer Review: Not commissioned; externally peer reviewed.

References / Referências

1. Hofland J, Herrera-Martínez AD, Zandee WT, de Herder WW. Management of carcinoid syndrome: a systematic review and meta-analysis. Endocr Relat Cancer. 2019;26:R145-R156. doi:10.1530/ERC-18-0495
2. Scholte A. Ein fall von angioma teleangiectaticum cutis mit chronischer endocarditis und malignem dünndarmcarcinoid. Beitrage Pathol Anat. 1931;86:440-443.
3. Halperin DM, Shen C, Dasari A, Xu Y, Chu Y, Zhou S, Shih YT, Yao JC. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. Lancet Oncol. 2017;18:525-34. doi: 10.1016/S1470-2045(17)30110-9.
4. Fröjd C, Larsson G, Lampic C, von Essen L. Health related quality of life and psychosocial function among patients with carcinoid tumours. A longitudinal, prospective, and comparative study. Health Qual Life Outcomes. 2007;5:1-9. doi:10.1186/1477-7525-5-18/TABLES/5
5. Beaumont JL, Cella D, Phan AT, Choi S, Liu Z, Yao JC. Comparison of health-related quality of life in patients with neuroendocrine tumors with quality of life in the general US population. Pancreas. 2012;41:461-6. doi:10.1097/MPA.0B013E3182328045
6. Pearman TP, Beaumont JL, Cella D, Neary MP, Yao J. Health-related quality of life in patients with neuroendocrine tumors: an investigation of treatment type, disease status, and symptom burden. Support Care Cancer. 2016;24:3695-703. doi:10.1007/S00520-016-3189-Z
7. Ito T, Lee L, Jensenc RT. Carcinoid-syndrome: recent advances, current status and controversies. Curr Opin Endocrinol Diabetes Obes. 2018;25:22. doi:10.1097/MED.0000000000000376
8. Gershon MD. 5-Hydroxytryptamine (serotonin) in the gastrointestinal tract. Curr Opin Endocrinol Diabetes Obes. 2013;20:14-21. doi:10.1097/MED.0B013E32835BC703
9. Jackson LN, Chen LA, Larson SD, Silva SR, Rychahou PG, Boor PJ, et al. Development and characterization of a novel in vivo model of carcinoid syndrome. Clin Cancer Res. 2009;15:2747-55. doi: 10.1158/1078-0432.CCR-08-2346.
10. Fanciulli G, Ruggeri RM, Grossrubatscher E, Calzo FL, Wood TD, Faggiano A, et al. Serotonin pathway in carcinoid syndrome: Clinical, diagnostic, prognostic and therapeutic implications. Rev Endocr Metab Disord. 2020;21:599-612. doi: 10.1007/s11154-020-09547-8.
11. Gustafsson BI, Tømmerås K, Nordrum I, et al. Long-term serotonin administration induces heart valve disease in rats. Circulation. 2005;111:1517-22. doi:10.1161/01.CIR.0000159356.42064.48
12. Koffas A, Toumpanakis C. Managing carcinoid heart disease in patients with neuroendocrine tumors. Ann Endocrinol. 2021;82:187-192. doi:10.1016/J.ANDO.2020.12.007
13. Laskaratos FM, Rombouts K, Caplin M, Toumpanakis C, Thirlwell C, Mandair D. Neuroendocrine tumors and fibrosis: An unsolved mystery? Cancer. 2017;123:4770-90. doi:10.1002/CNCR.31079
14. Clement D, Ramage J, Srirajaskanthan R. Update on Pathophysiology, Treatment, and Complications of Carcinoid Syndrome. J Oncol. 2020;:8341426.doi:10.1155/2020/8341426
15. Cunningham JL, Janson ET, Agarwal S, Grimelius L, Stridsberg M. Tachykinins in endocrine tumors and the carcinoid syndrome. Eur J Endocrinol. 2008;159:275-82. doi:10.1530/EJE-08-0196
16. Hannah-Shmouni F, Stratakis CA, Koch CA. Flushing in (neuro) endocrinology. Rev Endocr Metab Disord. 2016;17:373-380. doi:10.1007/S11154-016-9394-8/FIGURES/2
17. Boutzios G, Kaltsas G. Clinical Syndromes Related to Gastrointestinal Neuroendocrine Neoplasms. Front Horm Res. 2015;44:40-57. doi:10.1159/000382053
18. Ikizoğlu G. Red face revisited: Flushing. Clin Dermatol. 2014;32:800-8. doi:10.1016/J.CLINDERMATOL.2014.02.019
19. Öberg K. 45 – Neuroendocrine Tumors and Related Disorders. 14th ed.

Amsterdam: Elsevier; 2020. doi:10.1016/B978-0-323-55596-8.00045-0
20. Ohe MR von der, Camilleri M, Kvols LK, Thomforde GM. Motor dysfunction of the small bowel and colon in patients with the carcinoid syndrome and diarrhea. N Engl J Med. 1993;329:1073-8. doi:10.1056/NEJM199310073291503
21. Eads JR, Reidy-Lagunes D, Soares HP, Chan JA, Anthony LB, Halfdanarson TR, et al. Differential Diagnosis of Diarrhea in Patients With Neuroendocrine Tumors. Pancreas. 2020;49:1123-30. doi:10.1097/MPA.0000000000001658
22. Bhattacharyya S, Toumpanakis C, Caplin ME, Davar J. Analysis of 150 Patients With Carcinoid Syndrome Seen in a Single Year at One Institution in the First Decade of the Twenty-First Century. Am J Cardiol. 2008;101:378-381. doi:10.1016/J.AMJCARD.2007.08.045
23. Zuetenhorst JM, Bonfrer JM, Korse CM, Bakker R, van Tinteren H, Taal BG. Carcinoid heart disease: The Role of Urinary 5-Hydroxyindoleacetic Acid Excretion and Plasma Levels of Atrial Natriuretic Peptide, Transforming Growth Factor-B and Fibroblast Growth Factor Johanna. Cancer. 2003;97:1609-1615. doi:10.1002/CNCR.11226
24. Bhattacharyya S, Toumpanakis C, Chilkunda D, Caplin ME, Davar J. Risk Factors for the Development and Progression of Carcinoid Heart Disease. Am J Cardiol. 2011;107:1221-6. doi:10.1016/J.AMJCARD.2010.12.025
25. Kaltsas G, Caplin M, Davies P, Ferone D, Garcia-Carbonero R, Grozinsky-Glasberg S, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Pre- and Perioperative Therapy in Patients with Neuroendocrine Tumors. Neuroendocrinology. 2017;105:245-54. doi:10.1159/000461583
26. Del Olmo-García MI, Muros MA, López-de-la-Torre M, Agudelo M, Bello P, Soriano JM, et al. Prevention and Management of Hormonal Crisis during Theragnosis with LU-DOTA-TATE in Neuroendocrine Tumors. A Systematic Review and Approach Proposal. J Clin Med. 2020;9:1-16. doi:10.3390/JCM9072203
27. Grozinsky-Glasberg S, Davar J, Hofland J, Dobson R, Prasad V, Pascher A, et al. European Neuroendocrine Tumor Society (ENETS) 2022 Guidance Paper for Carcinoid Syndrome (CS) and Carcinoid Heart Disease (CHD). J Neuroendocrinol. 2022:e13146. doi:10.1111/JNE.13146
28. Corcuff JB, Chardon L, el Hajji Ridah I, Brossaud J. Urinary sampling for 5HIAA and metanephrines determination: revisiting the recommendations. Endocr Connect. 2017;6:R87-R98. doi:10.1530/EC-17-0071
29. Davar J, Connolly HM, Caplin ME, Pavel M, Zacks J, Bhattacharyya S, et al. Diagnosing and Managing Carcinoid Heart Disease in Patients With Neuroendocrine Tumors: An Expert Statement. J Am Coll Cardiol. 2017;69(10):1288-1304. doi:10.1016/J.JACC.2016.12.030
30. Wedin M, Mehta S, Angerås-Kraftling J, Wallin G, Daskalakis K. The Role of Serum 5-HIAA as a Predictor of Progression and an Alternative to 24-h Urine 5-HIAA in Well-Differentiated Neuroendocrine Neoplasms. Biology. 2021;10:76. doi: 10.3390/biology10020076.
31. Becker A, Schalin-Jäntti C, Itkonen O. Comparison of Serum and Urinary 5-Hydroxyindoleacetic Acid as Biomarker for Neuroendocrine Neoplasms. J Endocr Soc. 2021;5:1-7. doi:10.1210/jendso/bvab106
32. Bober B, Saracyn M, Kołodziej M, Kowalski Ł, Deptuła-Krawczyk E, Kapusta W,~et al. Carcinoid Heart Disease: How to Diagnose and Treat in 2020? Clin Med Insights Cardiol. 2020;14. doi:10.1177/1179546820968101
33. Dimitriadis GK, Weickert MO, Randeva HS, Kaltsas G, Grossman A. Medical management of secretory syndromes related to gastroenteropancreatic neuroendocrine tumours. Endocrine-Related Cancer. 2016;23(9):R423-R436. doi:10.1530/ERC-16-0200
34. Bouma G, van Faassen M, Kats-Ugurlu G, de Vries EGE, Kema IP, Walenkamp AME. Niacin (Vitamin B3) Supplementation in Patients with Serotonin-Producing Neuroendocrine Tumor. Neuroendocrinology. 2016;103:489-94. doi:10.1159/000440621
35. Fiebrich HB, van den Berg G, Kema IP, Links TP, Kleibeuker JH, Van Beek AP, et al. Deficiencies in fat-soluble vitamins in long-term users of somatostatin analogue. Aliment Pharmacol Ther. 2010;32:1398-404. doi:10.1111/J.1365-2036.2010.04479.X
36. Alonso-Gordoa T, Capdevila J, Grande E. GEP-NETs update: Biotherapy for neuroendocrine tumours. Eur J Endocrinol. 2015;172:R31-R46. doi:10.1530/EJE-14-0354
37. Kvols LK, Oberg KE, O'Dorisio TM, Mohideen P, de Herder WW, Arnold R, et al. Pasireotide (SOM230) shows efficacy and tolerability in the treatment of patients with advanced neuroendocrine tumors refractory or resistant to octreotide LAR: results from a phase II study. Endocr Relat Cancer. 2012;19:657-66. doi:10.1530/ERC-11-0367
38. Wolin EM, Jarzab B, Eriksson B, Walter T, Toumpanakis C, Morse MA, et al. Phase III study of pasireotide long-acting release in patients with metastatic neuroendocrine tumors and carcinoid symptoms refractory to available somatostatin analogues. Drug Des Devel Ther. 2015;9:5075-86. doi:10.2147/DDDT.S84177
39. Halperin DM, Huynh L, Beaumont JL, Cai B, Totev T, Bhak RH, et al. Impact of carcinoid syndrome symptoms and long-term use of somatostatin analogs on quality of life in patients with carcinoid syndrome A survey study. Medicine. 2018;97 :e13390.doi:10.1097/MD.0000000000013390
40. Blot K, Duchateau L, Lescrauwaet B, Liyanage N, Ray D, Mirakhur B, et al. A Patient-Reported Outcomes Analysis Of Lanreotide In The Treatment Of NETs Patients With Carcinoid Syndrome: Evidence From The ELECT Trial. Patient Relat Outcome Meas. 2019;10:335-43. doi:10.2147/PROM.S219982
41. Kulke MH, Hörsch D, Caplin ME, Anthony LB, Bergsland E, Öberg K, et al. Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome. J Clin Oncol. 2017;35:14-23. doi:10.1200/JCO.2016.69.2780
42. Cella D, Beaumont JL, Hudgens S, Marteau F, Feuilly M, Houchard A, et al. Relationship Between Symptoms and Health-related Quality-of-life Benefits in Patients With Carcinoid Syndrome: Post Hoc Analyses From TELESTAR. Clin Ther. 2018;40:2006-2020.e2. doi:10.1016/J.CLINTHERA.2018.10.008
43. Hörsch D, Anthony L, Gross DJ, Valle JW, Welin S, Benavent M, et al. Long-term treatment with telotristat ethyl in patients with carcinoid syndrome symptoms: results from the TELEPATH study. Neuroendocrinology. 2022;112:298. doi:10.1159/000516958
44. Saavedra C, Barriuso J, McNamara MG, Valle JW, Lamarca A. Spotlight on telotristat ethyl for the treatment of carcinoid syndrome diarrhea: patient selection and reported outcomes. Cancer Manag Res. 2019;11:7537-56. doi:10.2147/CMAR.S181439
45. Hofland LJ, de Herder WW, Waaijers M, Zuijderwijk J, Uitterlinden P, van Koetsveld PM, et al. Interferon-alpha-2a is a potent inhibitor of hormone secretion by cultured human pituitary adenomas. J Clin Endocrinol Metab. 1999;84:3336-43. doi:10.1210/JCEM.84.9.6005
46. Oleinikov K, Korach A, Planer D, Gilon D, Grozinsky-Glasberg S. Update in carcinoid heart disease - the heart of the matter. Rev Endocr Metab Disord. 2021;22:553-61. doi:10.1007/s11154-020-09624-y/Published
47. Strosberg J, Wolin E, Chasen B, Kulke M, Bushnell D, Caplin M, et al. Health-related quality of life in patients with progressive midgut neuroendocrine tumors treated with 177 Lu-Dotatate in the Phase III NETTER-1 Trial. J Clin Oncol. 2018;36:2578-84. doi:10.1200/JCO.2018.78.5865
48. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 Trial of 177 Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med. 2017;376:125-35. doi:10.1056/NEJMOA1607427
49. Cives M, Strosberg J. Radionuclide therapy for neuroendocrine tumors. Curr Oncol Rep. 2017;19:9. doi:10.1007/S11912-017-0567-8
50. Strosberg JR, Caplin ME, Kunz PL, Ruszniewski PB, Bodei L, Hendifar A, et al. 177Lu-Dotatate plus long-acting octreotide versus high dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. Lancet Oncol. 2021;22:1752-63. doi:10.1016/S1470-2045(21)00572-6
51. Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016;387:968-77. doi:10.1016/S0140-6736(15)00817-X
52. Pavel ME, Hainsworth JD, Baudin E, Peeters M, Hörsch D, Winkler RE, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet. 2011;378:2005-12. doi:10.1016/S0140-6736(11)61742-X
53. Jin C, Nair A, Balasingam S, Majid M, Al Chalaby S, Takahashi N, et al. Carcinoid Heart Disease: Pathophysiology, Pathology, Clinical Manifestations, and Management. Cardiology. 2021;146:65-73. doi:10.1159/000507847
54. Davis LM, Nicou N, Martin W, Corcoran B, Mulholland N, Srirajaskanthan R, et al. Timing of peptide receptor radiotargeted therapy in relation to cardiac valve surgery for carcinoid heart disease in patients with neuroendocrine metastases and cardiac syndrome. A single-centre study from a centre of excellence. Nucl Med Commun. 2020;41:575-81. doi:10.1097/MNM.0000000000001200
55. Hicks RJ, Kwekkeboom DJ, Krenning E, Komminoth P, Kos-Kudła B, de Herder WWet al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasms: Peptide Receptor Radionuclide Therapy with Radiolabelled Somatostatin Analogues. Neuroendocrinology. 2017;105:295-309. doi:10.1159/000475526

56. Bernheim AM, Connolly HM, Rubin J, Møller JE, Scott CG, Nagorney DM, et al. Role of Hepatic Resection for Patients With Carcinoid Heart Disease. Mayo Clin Proc. 2008;83:143-50. doi:10.4065/83.2.143
57. Bernheim AM, Connolly HM, Hobday TJ, Abel MD, Pellikka PA. Carcinoid Heart Disease. Progr Cardiovasc Dis. 2007;49:439-51. doi:10.1016/J.PCAD.2006.12.002
58. Askew JW, Connolly HM. Carcinoid valve disease. Curr Treat Options Cardiovasc Med. 2013;15:544-55. doi:10.1007/S11936-013-0265-2/FIGURES/1
59. Bonou M, Kapelios CJ, Kaltsas G, Perreas K, Toutouzas K, Barbetseas J. Cardiac surgery for carcinoid heart disease: a weapon not to be misused. Cardiology. 2017;136:243-51. doi:10.1159/000450938
60. Hart EA, Meijs TA, Meijer RCA, Dreijerink KM, Tesselaar ME, de Groot CA, et al. Carcinoid heart disease: a guide for screening and timing of surgical intervention. Neth Heart J. 2017;25:471-8. doi:10.1007/S12471-017-1011-2