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Carcinoid Syndrome: Diagnosis and Medical Management

ABSTRACT

Gastro-intestinal carcinoids are slow growing tumors arising from enterochromaffin or Kulchitsky cells. Their clinical presentation depends on what combination of bioactive substances is secreted. Midgut carcinoid can present with the carcinoid syndrome in the presence of liver metastases. Its most typical clinical manifestations include cutaneous flushing and diarrhea. A nonspecific biochemical tumor marker for carcinoid tumors is serum chromogranin A and a specific marker for the carcinoid syndrome is the increased urinary excretion of 5-hydroxy indole acetic acid (5-HIAA). Localizing studies in carcinoid tumors/syndrome are: transabdominal ultrasonography (US), endoscopy, endoscopic US, videocapsule endoscopy, computerized tomography, magnetic resonance imaging, selective abdominal angiography, ^{111}In-pentetreotide scintigraphy (and intraoperative radionuclide probe), [123]I (^{131}I)-metaiodobenzylguanidine (MIBG) scintigraphy, bone scintigraphy and ^{11}C-5-HT positron emission tomography (PET). Therapies for carcinoid tumors/syndrome are: surgery, somatostatin analogs, interferon-alpha, radiotherapy, liver dearterialization, liver (chemo, or radio)-embolization, alcohol sclerotherapy of liver metastases, radiofrequency ablation of liver metastases, cryosurgery of liver metastases, occasionally liver transplantation, radiotherapy-coupled somatostatin analogs, ^{131}I-MIBG and occasionally chemotherapy. **(Arq Bras Endocrinol Metab 2005;49/5:850-860)**

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RESUMO

Síndrome Carcinóide: Diagnóstico e Manejo Clínico.
Carcinóides gastro-intestinais são tumores de crescimento lento originários das células enterocromafínicas ou de Kulchitsky. Sua apresentação clínica depende das combinações de substâncias bioativas que são secretadas. Carcinóides de intestino delgado podem se apresentar com síndrome carcinóide na presença de metástases hepáticas. A manifestação clínica típica inclui *flushing* cutâneo e diarréia. A cromogranina-A é um marcador bioquímico tumoral inespecífico de tumores carcinóides e o aumento da excreção urinária de ácido 5-hidroxiindolacético (5-HIAA), um marcador específico para a síndrome carcinóide. Estudos de localização nos tumores/síndrome carcinóide são: ultrassonografia (US) abdominal, endoscopia, US endoscópica, endoscopia com vídeo-cápsula, tomografia computadorizada, ressonância magnética, angiografia abdominal seletiva, cintilografia com ^{111}In-pentetreotide (e sonda radioisotópica intraoperatória), cintilografia com [123]I (^{131}I) -metaiodobenzilguanidina (MIBG), cintilografia óssea e tomografia por emissão de pósitron (^{11}C-5-HT). Tratamento para tumores/síndrome carcinóide são: cirurgia, análogos de somatostatina, interferon-alfa, radioterapia, embolização arterial hepática, quimioembolização hepática, escleroterapia alcoólica de metástases hepáticas (MH), ablação por radiofreqüência de MH, criocirurgia de

HISTORICAL OVERVIEW

GASTRO-INTESTINAL CARCINOIDS are slow growing neoplasms as compared with adenocarcinomas, but they can also behave aggressively. They are derived from neoplastic proliferation of enterochromaffin (ECL) or Kulchitsky cells (1).

In 1888, Lubarsch first described a patient with multiple carcinoids of the ileum but regarded them as carcinomas (2). Two years later, Ransom first described the classical symptomatology of the carcinoid syndrome in a patient with an ileal carcinoid tumor and hepatic metastasis (3). However, it was Oberndorfer in 1907, who coined the term "karzinoide" to describe these tumors, which he believed to behave in a more benign fashion than adenocarcinomas (4). In 1963, Williams and Sandler classified carcinoids according to their embryologic site of origin as foregut carcinoids (respiratory tract, stomach, duodenum, biliary system, and pancreas), midgut carcinoids (small intestine, appendix, cecum, and proximal colon), and hindgut carcinoids (distal colon and rectum) (5). However, these lesions exhibit a high degree of morphologic and biologic heterogeneity and a more generic term, neuroendocrine tumor (NET) has been introduced to replace the term carcinoid. Such lesions are currently referred to as gastroenteropancreatic (GEP) NETs (GEP-NETs). According to the WHO classification, distinction was made between well-differentiated NETs (benign behavior or uncertain malignant potential), well-differentiated neuroendocrine carcinomas (low-grade malignancy), and poorly differentiated (usually small cell) neuroendocrine carcinomas of high-grade malignancy. Nevertheless, the term carcinoid was not abandoned and for GEP-NETs, it is used synonymously with the term "well-differentiated NET". The term "malignant carcinoid" is used synonymously with the term well-differentiated neuroendocrine carcinoma (6). The differentiation is based on tumor morphology, tumor size (in general larger tumors are more aggressive), and the presence or absence of local invasion and/or metastasis, thus reflecting biological behavior. Most NETs are well-differentiated tumors that are characterized by a solid trabecular or glandular struc-

ture, tumor cell monomorphism with absent or low cytological atypia, and a low mitotic (< 2 mitoses/mm^2) and proliferative status ($< 2\%$ Ki-67 positive cells). Only in the presence of metastasis and/or invasiveness is the tumor defined as a well-differentiated neuroendocrine carcinoma. Poorly differentiated NETs are invariably malignant, are defined as poorly differentiated neuroendocrine carcinomas, and are characterized by a predominantly solid structure with abundant necrosis, cellular atypia with a high mitotic index (≥ 10 mitoses/mm^2) and proliferative status ($> 15\%$ Ki-67 positive cells), diffuse reactivity for cytosolic markers, and scant or weak reactivity for granular markers or neurosecretory products (1).

Carcinoid lesions are the most common NETs and compose approximately 50% of all NETs of the gastrointestinal tract. In most instances, they are discovered incidentally at the time of surgery for other abdominal disorders. Their presence may be undetectable for years without obvious signs or symptoms. Evidence for this observation is supported by their relatively high incidence in large autopsy series (7). When symptoms do occur, they are due either to local tumor mass effects, the effects of tumor-engendered fibrosis, or to the secreted bioactive products from the neoplasm. Symptoms caused by local tumor effects include vague abdominal pain (invasion, intussusception, fibrous adhesions, hypermotility), which is often undiagnosed or leads to erroneous diagnoses like irritable bowel syndrome (8,9).

Carcinoids have protean clinical presentations, depending on what combination of bioactive substances is secreted. One of their main characteristics of the enterochromaffin (ECL) or Kulchitsky cells is the synthesis, storage, and secretion of serotonin. Serotonin (5-hydroxytrypamine, 5-HT) is synthesized from tryptophan through its precursor, 5-hydroxy tryptophan (5-HTP), and subsequently metabolized to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted in the urine. In addition to serotonin, carcinoid tumors may also secrete other hormones such as corticotrophin (ACTH), histamine, dopamine, substance P, neurotensin, prostaglandins, kallikrein, and tachykinins. In normal subjects, approximately 99% of tryptophan is used for the synthesis of nicotinic acid (niacin), and 1% or less is converted to 5-HT. In patients with carcinoid tumors, there is a shift toward the production of 5-HT and eventually 5-HIAA. This may lead to tryptophan deficiency and pellagra might ensue as a result of nicotinic acid deficiency (9). When 5-HT and other products are secreted into the portal circulation, they are efficiently metabolized by the liver

and do not usually cause any systemic signs or symptoms. However, when liver metastases are present or when the primary lesions are found in the bronchus and/or ovaries, the systemic features of the carcinoid syndrome become more evident. This classical syndrome occurs in fewer than 10% of patients, and its most typical clinical manifestations include cutaneous flushing most commonly of the face, neck, and upper chest and diarrhea, occurring in up to 75%. Less frequent manifestations include cardiac valvular abnormalities (plaque-like, fibrous endocardial thickening that principally involves the right side of the heart (causing tricuspid regurgitation tricuspid stenosis, pulmonary regurgitation, and pulmonary stenosis), bronchoconstriction and (as already mentioned) pellagra. Foregut carcinoids can secrete 5-HTP, histamine and polypeptide hormones like ACTH. The can produce a characteristic clinical syndrome known as "atypical" carcinoid syndrome. Midgut carcinoids release 5-HT and other vasoactive compounds such as kinins, prostaglandins, and substance P and they are more likely to cause the classic carcinoid syndrome with the development of hepatic metastases. Hindgut carcinoid tumors rarely contain 5-HT and usually do not present with the carcinoid syndrome; however. The symptoms of the carcinoid syndrome can be both of variable intensity as well as paroxysmal, responding intermittently to a particular "trigger" agent, such as alcohol, cheese, coffee (these are serotonin-rich foods), or exercise (8,10,11).

Many carcinoid tumors exhibit a significant association with other non-carcinoid tumors of various histological types. A relatively large percentage of carcinoids are multicentric.

Because carcinoid tumors frequently present with obscure clinical manifestations, numerous investigatory procedures are often undertaken prior to establishing the correct diagnosis. Although clinical diagnosis is based on symptoms, biochemical confirmation is necessary. The diagnostic strategies employed usually depend on the individual clinical presentation (8,10,11).

Biochemical markers

24-hour urinary excretion of 5-hydroxy indole acetic acid (5-HIAA)

The measurement of 24-hour urinary excretion of 5-HIAA is useful because it provides a summation of tumor secretory activity that may occasionally be missed by random plasma peptide sampling if secretion is paroxysmal. The test specificity is approximately 88%.

Certain serotonin-rich foods (bananas, avocados, plums, eggplant, tomatoes, plantain, pineapples, kiwis and walnuts) can increase urinary 5-HIAA levels and should be avoided during specimen collection (12-14).

Chromogranin A

Chromogranin A (CgA) is a member of the chromogranin family, which is stored in the secretory granules of neuroendocrine cells. Because CgA is a constitutive secretory product of most NETs, its detection in plasma can be utilized as a general tumor marker for carcinoids and even for "non-functioning" tumors. In carcinoid tumors, the highest concentrations of CgA were noted in metastatic midgut lesions with CgA elevation in 87% of lesions, whereas 5-HIAA increases was noted in 76%. CgA concentration correlated with tumor burden. Plasma CgA levels are sensitive but nonspecific markers of carcinoid tumors because they are also elevated in pancreatic NETs, as well as in other types of NETs. False-positive increased CgA concentrations can be seen in renal impairment, liver failure, atrophic gastritis, and inflammatory bowel disease (15).

If biochemical results are equivocal, these tests should be repeated and plasma CgA measured because it is the most sensitive and reliable screening test.

Localization studies

If one of the peptides/amines or its breakdown products are initially elevated, the precise localization of the primary lesion and its metastases should be undertaken, starting with ^{111}In-labelled pentetreotide scintigraphy (16).

Table 1. Localizing studies in carcinoid tumors/the carcinoid syndrome.

Morphological
Transabdominal ultrasonography
Endoscopy
Endoscopic ultrasonography
Videocapsule endoscopy
Computerized Tomography (CT)
Magnetic Resonance Imaging (MRI)
Selective abdominal angiography

Functional
[111]In-pentetreotide scintigraphy
[123]I (^{131}I) - metaiodobenzylguanidine (MIBG) scintigraphy
Bone scintigraphy
Positron emission tomography (PET)
Intraoperative radionuclide probe

Miscellaneous
Echocardiography

Nuclear medicine

[111]In-labelled pentetreotide scintigraphy

[111]In-labelled pentetreotide shares the receptor-binding profile of Octreotide and Lanreotide (see later), rendering it an ideal radiopharmaceutical for imaging of somatostatin receptor subtype (sst) 2- (and 5) (sst_2 and sst_5)-positive (see later) tumors (17). The sensitivity of the study can be enhanced by the simultaneous use of single positron emission computed tomography (SPECT) imaging (17). The overall sensitivity of ^{111}In-labelled pentetreotide scintigraphy is approximately 80% to 90%, and it is effective in detecting primary and metastatic lesions not apparent by conventional radiologic-imaging techniques) (18,19). ^{111}In-labelled pentetreotide scintigraphy should be used as the initial imaging method in patients with carcinoid tumors (figure 1). Of particular advantage is the fact that one scan images the entire body; thus covert metastases may be identified. Intraoperative g detection has been considered as theoretically additional to external ^{111}In-labelled pentetreotide scintigraphy in the detection of small endocrine lesions, but high-background uptake (kidneys, liver, and spleen) and inadequate collimators have considerably limited its general utility (20).

Bone scintigraphy

Bone scintigraphy with [99m]TcMDP is the mainstay for identifying bone metastases associated with NETs, with reported detection rates above 90%. Two studies that utilized ^{111}In-labeled pentetreotide demonstrated similar diagnostic rates, ranging between 60% and 100% (21,22).

Radiolabelled metaiodobenzylguanidine (MIBG)

Metaiodobenzylguanidine (MIBG) is a guanidine derivative that exploits the specific type 1 amine uptake mechanism at the cell membrane and storage within the intracellular storage vesicles. Several NETs including carcinoids exhibit this specific uptake mechanism and can thus accumulate MIBG. Scanning with radiolabelled metaiodobenzylguanidine ([123]I-, or ^{131}I-MIBG) has an overall sensitivity ranging from 55% to 70%, with a specificity of 95%. ^{111}In-pentetreotide scintigraphy is generally more sensitive than [123]I-, or ^{131}I-MIBG scintigraphy (21,23).

Positron emission tomography (PET)

Positron emission tomography (PET) is a relatively novel, noninvasive technique that facilitates biochemical and metabolic studies of human tumors. Because neoplastic cells are characterized by a higher glycolytic rate than normal cells, the use of [^{18}F] fluoro-2-deoxy-glucose (FDG) was initially used in biochemical imaging for the diagnosis and staging of cancer. However, as already stated, most NETs (and carcinoids) are well differentiated and slow growing, they have a low metabolic rate and cannot be visualized efficiently with this tracer, as evidenced by detection rates ranging between 25% and 73%. Because carcinoid tumors characteristically synthesize serotonin, the administration of radioactive serotonin precursor ^{11}C-5-HT has been shown to provide excellent tumor visualization, with high detection rates (24,25). More recently, ^{68}Ga coupled to Octreotide has been used as tracers for PET imaging, also achieving high detection rate (26). PET should, therefore, be considered still as an investigational yet very promising
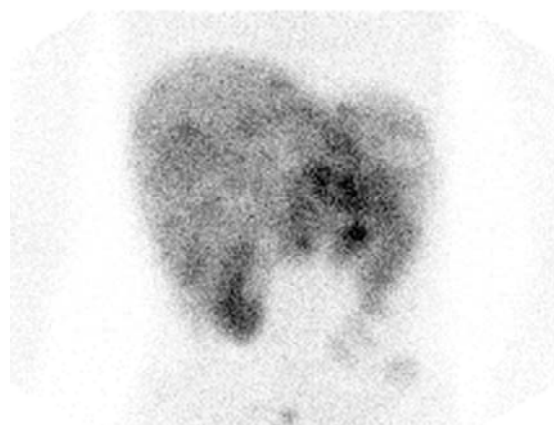

Figure 1. Planar ^{111}In-pentetreotide scintigraphy **(left)** and transverse abdominal CT **(right)** images showing extensive somatostatin receptor-positive liver metastases in a patient with a metastatic midgut carcinoid and the carcinoid syndrome.

method for carcinoid imaging.

Endoscopy, endoscopic ultrasound and videocapsule endoscopy

Upper and lower gastrointestinal endoscopy

Upper gastrointestinal endoscopy can identify lesions as far as the ligament of Treitz and lower and lower gastrointestinal endoscopy can detect some terminal ileal tumors as well as colon and rectal carcinoids.

Endoscopic ultrasound

Endoscopic ultrasound is a highly sensitive method for detecting carcinoid tumors of the stomach and duodenum and is superior to conventional ultrasound, particularly in the detection of small lesions localized to the bowel wall because it can detect luminal lesions as small as 2 to 3mm in size (27).

Videocapsule endoscopy

(Video)capsule endoscopy has obvious potential for surveillance of the small intestine for carcinoid tumors (28,29).

Radiology

Ultrasonography, computerized tomography (CT), magnetic resonance imaging (MRI) and angiography

Additional studies such as transabdominal ultrasonography, triple-phase helical computerized tomography (CT), magnetic resonance imaging (MRI), and selective mesenteric angiography may identify an additional 10% to 15% of primaries but are probably only justified if surgery is contemplated and more precise topographic delineation considered necessary to define resection.

Transabdominal ultrasound identifies approximately one third of small bowel carcinoids and two thirds of liver metastases, and may also be used to guide percutaneous biopsies of liver tumors (30,31).

Mass lesions and evidence of calcification and fibrosis define CT scan and MRI findings associated with carcinoid tumors. Radiating strands of fibrosis and spiculation are characteristic hallmarks, especially in conjunction with a mass lesion. The degree of radiating strands detected by CT tends to increase with the degree of fibrosis seen histopathologically, and mesenteric fibrosis may lead to traction or fixation of the bowel (32). Mesenteric lymph node metastases are evident on CT scans in 91% (33). MRI and CT provide important means of initial localization of carcinoid tumors or their metastases; however, their detection rates and sensitivities are lower than imaging with

[111]In-pentetreotide scintigraphy. Median detection rate and sensitivity of CT and/or MRI are about 80%, in contrast to 89% detection rate and 84% sensitivity with ^{111}In-pentetreotide scintigraphy. The diagnostic efficacy of either CT or MR does not differ much. The reported detection rates of CT alone range between 76% and 100%, whereas MRI alone reported rates are between 67% and 81%.

Angiographic changes are distinctive, with narrowing or occlusion of the distal ileal arcade and stenosis of the intramesenteric arteries being a characteristic finding.

Importantly, patients with equivocal biochemistry, negative nonspecific markers, and negative ^{111}In-pentetreotide scintigraphy should probably not be further investigated but instead followed up annually.

Therapy

Surgery

Surgery is generally regarded as the most effective treatment for both local tumor effects (obstruction, bleeding, and perforation) and symptoms caused by the secretory agents because it removes the primary lesion and decreases levels of bioactive agents (16,34-37). In essence, surgery may be categorized as:

Adequate resection with curative or palliative intent for primary and regional lesions;

Surgical resection of regional or distant metastatic disease with cytoreductive intent; and

Resection of disease for symptom palliation without cytoreductive intent (35-37).

If residual tumor is present after surgery (liver, lymph nodes, peritoneal), long-acting somatostatin analogs (see later) have proven efficacious in the management of carcinoid syndrome symptomatology (16,36-38).

Hepatic metastases can be resected because debulking (cytoreductive surgery) may reduce the symptoms, facilitate pharmacologic management, and improve survival (39). Liver transplantation is occasionally successful, but should only be performed when the presence of extrahepatic tumors has been ruled out (16,34,36).

(Chemo- and radio-)embolization

Similar to debulking surgery, hepatic artery occlusion, either by ligation, embolization, or chemoembolization, is beneficial or decreases symptoms of carcinoid syndrome, with tumor regression in 65% of patients. However, the duration of palliation may be limited because of either recurrence or rearterialization of

Table 2. Therapy of carcinoid tumors/the carcinoid syndrome.

Surgical
Curative
Cytoreductive debulking

Medical
Symptomatic
Somatostatin analogs
Interferon-alpha
(Chemotherapy)

Radiotherapy
In the presence of liver metastases
Liver transplantation
Interventional tumor debulking
Liver dearterialization
(Chemo, or radio)-embolization
Alcohol sclerotherapy

Radiofrequency ablation
Cryosurgery
Radiotherapy-coupled somatostatin analogs
^{131}I-MIBG

lesions. Hepatic artery embolization combined with sequential chemotherapy has been more encouraging, resulting in a reduction of tumor size in 78% of patients (40). Similarly, embolization with Yttrium-labeled microspheres has been useful in some circumstances (41).

Cryosurgical debulking or radiofrequency ablation

Cryosurgical debulking or radiofrequency ablation (RFA) of hepatic carcinoid metastases have been described as of some benefit for palliation of carcinoid syndrome, but their efficacy remains to be rigorously evaluated (35,42,43).

Chemotherapy

Conventional chemotherapeutic agents such as streptozotocin, 5-FU, doxorubicin, and cyclophosphamide alone have used in the pasted and have yielded disappointing results, with an overall 20%–40% response rate. Etoposide may be marginally more effective either alone or in combination with cisplatin. Currently, the indications for chemotherapy need to be very carefully reconsidered, because biotherapy with somatostatin analogs and/or interferon alpha can control the symptoms of humoral syndromes and may also affect tumor growth. However, chemotherapy may be beneficial for selected cases of advanced tumors that do not respond to other forms of therapy, and for

poorly differentiated NETs (16,44,45).

Medical therapy

Somatostatin analogs

Somatostatin is a small cyclic peptide. It circulates in the blood in two biologically active forms: somatostatin-14 and somatostatin-28. Somatostatin inhibits a variety of physiological functions in the gastrointestinal tract, like gastrointestinal motility, gastric acid production, pancreatic enzyme secretion, and bile and colonic fluid secretion. It inhibits the secretion of pancreatic and intestinal hormones like insulin, glucagon, secretin, and vasoactive intestinal polypeptide (46). However, the multiple simultaneous effects of pharmacological concentrations of somatostatin in different organs, the need for intravenous administration, the short duration of action and the post-infusion rebound hypersecretion of hormones considerably hampered its clinical use (47). Somatostatin acts through high-affinity G protein-coupled membrane receptors.

Five somatostatin receptor (sst) subtype genes have been cloned and characterized. They were code-named sst_1, sst_2, sst_3, sst_4, and sst_5. Tumors arising from somatostatin-target tissues, frequently express a high density of ssts. The five sst subtypes all bind somatostatin with high affinity. The sst_1 and sst_4 receptors do not bind the currently available octapeptide somatostatin-analogs Octreotide and Lanreotide (see later), whereas sst_{2A}, sst_3, and sst_5 receptors display a high, low, and moderate affinity, respectively, toward these octapeptide somatostatin-analogs. The predominant expression of sst_2 receptors on carcinoid tumors forms the basis for the successful clinical application of these octapeptide somatostatin-analogs in controlling symptoms related to hormonal hypersecretion (47-49). The high density of ssts on these tumors further allows the use of radiolabelled somatostatin-analogs like ^{111}In-pentetreotide to visualize these sst-positive tumors *in vivo* (see earlier). Octreotide (Sandostatin) was the first octapeptide somatostatin analog that was synthesized. Its elimination half-life after subcutaneous administration is two hours, and rebound hypersecretion of hormones does not occur. Octreotide binds only with a high affinity to sst_2 and sst_5. Other cyclic analogs with almost similar affinity and activity profiles, like Lanreotide (Somatuline) have been developed subsequently (47). Octreotide and Lanreotide have been registered in most countries for the control of hormonal symptoms in patients with carcinoids. Lanreotide does not differ significantly from Octreotide in treatment of carcinoid symptoms.

Octreotide can be administered by multiple subcutaneous injections or by continuous subcutaneous infusion as well as by the intravenous route, either as a single injection or as a continuous infusion over many hours or days. The slow-release depot intramuscular formulation of Octreotide (Sandostatin LAR) has to be administered once every 4 weeks and that of Lanreotide (Lanreotide-PR) has to be administered once every 2 weeks. A new slow-release depot preparation of Lanreotide, Somatuline Autogel, has been introduced in several European countries. This drug has to be administered deep subcutaneously once every 4 weeks. The introduction of these long-acting somatostatin analogs and depot administration has facilitated the control of most carcinoid syndrome symptoms and greatly improved quality of life. Dosages of Octreotide and Lanreotide can be adjusted in accordance with clinical successful control (8,16,38,50).

Somatostatin analogs decrease the release of bioactive secreted products with effective resolution of flushing and diarrhea in between 70% and 80% of patients. Although biochemical response rates ranged from 0% to 77%, tumor response rates were very low (0%–9%) (8,16,37,50-54).

Only modest adverse effects have been reported like: nausea, cramps, loose stools, mild steatorrhea, biliary sludge, or cholelithiasis (in up to 50% of patients but only 1% with acute symptoms warranting cholecystectomy), impaired glucose tolerance, local pain and erythema at injection site and very rarely gastric atony (37,50-54). Intravenous Octreotide is particularly effective in the management of a "carcinoid crisis," which is usually engendered by anesthesia, surgical, or radiologic intervention. This life-threatening clinical condition is characterized by profound hypotension and tachycardia often associated with mortality without rapid preemptive pharmacologic intervention (55).

Interferon alpha

Recombinant leukocyte interferon-a may be of some use in the treatment of disseminated carcinoid tumors and carcinoid syndrome. The precise mechanism of action is not well understood but may include direct inhibition of cell proliferation, immune cell-mediated cytotoxicity, inhibition of angiogenesis, and induction of differentiation via cell cycle block (56). Although these agents are more toxic than somatostatin analogs, they may exhibit greater antitumor activity, but substantial adverse effects include fever, fatigue, anorexia, and weight loss as well as alopecia, autoimmune diseases and myelosuppression. In patients with the carcinoid syndrome, biochemical response rates ranged from 7% to 53%, and objective tumor response rates ranged from 7% to 20% (57,58).

There was little advantage in the use of a combination of Octreotide and interferon-a in patients in whom Octreotide alone or interferon-a produced no benefit. Although biochemical responses were reported in 72–77%, no objective tumor regression was observed. It is debatable whether somatostatin analogs and interferon-a exhibit a synergistic effect in carcinoid syndrome symptom management (56,58).

Supportive care

Supportive care of carcinoid tumors or carcinoid syndrome includes avoiding stress and conditions or substances that precipitate symptoms; dietary supplementation with nicotinamide is also recommended. Mild diarrhea responds to antidiarrheal agents, such as loperamide, or opiates and bronchoconstriction to bronchodilators that interact with α-adrenergic receptors. Cyproheptadine decreases diarrhea in 50%, but adverse effects (20%) can be prohibitive. Cardiac failure may require diuretics and even valve replacement. Some brief relief with prednisone has been reported. Overall somatostatin analog therapy has supplanted most other medication (8,16,37,38,59).

Peptide receptor radionuclide therapy (prrt)

In general, carcinoids are resistant to radiotherapy, although external beam therapy has been used for palliation of bone metastases and the management of spinal cord compression and brain metastases. More recently, systemic peptide receptor radionuclide therapy (prrt) has been introduced for inoperable or metastasized GEP NETs (60). In general, sst-agonist complexes follow the mechanism and route of internalization as described for many other G protein-coupled receptor complexes. The predominant expression of sst_2 receptors in most sst-positive endocrine tumors and the efficiency of sst_2 receptors to undergo agonist-induced internalization are very important for the radiotherapeutic application of radiolabelled octapeptide somatostatin-analogs. However, [^{111}In-DTPA^0] Octreotide may not be the most suitable compound to carry out radiotherapy because the Auger electrons emitter ^{111}In has a low tissue penetration. In addition, a stable coupling of α- or α-emitting isotopes to [DTPA^0]Octreotide could not be achieved, which initiated the development of a novel compound, like [DOTA^0,Tyr^3]Octreotide, allowing a stable binding with the α-emitter yttrium-90 (^{90}Y) [^{90}Y-DOTA^0, Tyr^3]Octreotide (^{90}Y-DOTATOC; OctreoTher®), and lutetium 177 ([^{177}Lu-DOTA^{0}Tyr^3]Octreotate). Fur-

thermore, $[^{111}In\text{-}DOTA^0]$Lanreotide and $[^{90}Y\text{-}DOTA^0]$Lanreotide can also be used for radiotherapy of sst_2- and sst_5-positive advanced, or metastatic endocrine tumors (61-64).

Initial studies with high dosages of ^{111}In-pentetreotide in patients with metastasized NETs were encouraging but partial remissions exceptional. On average, response rates were between 13% and 20% The subsequent use of $[^{90}Y\text{-}DOTA^0,Tyr^3]$Octreotide have suggested increased efficacy with some partial remissions (10% and 30%). The effects of radionuclide therapy are better at maintaining the status quo, with 53% and 79% of patients achieving biochemical or tumor size stability, respectively. The newest radiolabelled somatostatin analog $[^{177}Lu\text{-}DOTA^0,Tyr^3]$ octreotate, which has a higher affinity for sst_2 has resulted in complete or partial responses in 28% of patients and tumor responses in 38% of patients, respectively. In these studies, tumor regression was positively correlated with a high uptake on the ^{111}In-pentetreotide scintigraphy, limited hepatic tumor mass, and high Karnofsky performance score. Overall symptomatic improvement as well as improvement in quality of life (65) may occur with either ^{111}In, ^{90}Y, or ^{177}Lu-labeled somatostatin analogs that have been used for prrt, but the results obtained with $[^{90}Y\text{-}DOTA^0,Tyr^3]$Octreotide and $[^{177}Lu\text{-}DOTA^0,Tyr^3]$ octreotate are more encouraging in terms of tumor regression. Issues of concern are renal damage (but this can be decreased by a pre-therapy amino acid infusion, which produces an added degree of kidney protection) and induction of myeloproliferative disorders (which is more prevalent in patients pre-treated with chemotherapy) (66). Because the acute adverse effects of this type of therapy are few and mild and the duration of the therapy response for radiopharmaceuticals more than 2 years, this therapeutical modality is increasingly accepted as standard therapy.

^{131}I-MIBG therapy

As already mentioned, more than 70% of carcinoids concentrate MIBG. The use of ^{131}I-MIBG therapy can be considered early in an adjuvant setting, after surgery to eradicate occult disease, or later for treatment of disseminated disease. Using this radiopharmaceutical an objective tumor response was recorded in 15%, with a symptomatic response in 65% of the patients (67).

New therapeutical developments

In recent years, many new sst selective analogs have been synthesized. A new so-called "universal" somatostatin analog, named SOM230, with high affinity for sst_1, sst_2, sst_3, and sst_5 receptors has been is currently under evaluation in phase II-III trials (68,69). New fundamental insights in receptor physiology also opened the concept of multi-receptor family cross talk, like between somatostatin and dopamine receptors and focus has also been addressed to the development of new drugs interacting with these phenomenons (70). In the near future it will become clear whether new bispecific or more universal somatostatin-analogs are indeed effective in tumors resistant to the current clinically available octapeptide analogs Octreotide and Lanreotide and can prevent endocrine tumors from tachyphylaxis to treatment (71). Like peptide receptor radionuclide therapy, peptide receptor-targeted chemotherapy to deliver the chemotherapeutic compounds selectively to tumor cells might be a promising approach as well (72,73). Newer radiopharmaceuticals as well as combinations will also be tested for peptide receptor radionuclide therapy. Radiolabelled agonists and antagonists of peptide receptors other than the somatostatin receptors [like: vasoactive intestinal polypeptide (VIP) receptor subtype VPAC1, cholecystokinin (CCK) and gastrin receptor subtypes CCK2 (CCK-B) and CCK1 (CCK-A), bombesin and gastrin-releasing peptide (GRP) receptor subtypes (BB1, BB2, BB3 and BB4), neuromedin B receptors, neurotensin receptors (like the receptor subtype NRT1), substance P (like the receptor subtype NK1) and neuropeptide Y receptors] are currently being investigated and might become available as well as therapies for carcinoid tumors and the carcinoid syndrome (74).

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