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REVIEW

Neuroendocrine tumors of the gastro-entero-pancreatic system

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Abstract

Gastro-entero-pancreatic (GEP) neuroendocrine tumors (NETs) are rare neoplasms, although their prevalence has increased substantially over the past three decades. Moreover, there has been an increased clinical recognition and characterization of these neoplasms. They show extremely variable biological behavior and clinical course. Most NETs have endocrine function and secrete peptides and neuroamines that cause distinct clinical syndromes, including carcinoid syndrome; however, many are clinically silent until late presentation with mass effects. Investigation and management should be individualized for each patient, taking into account the likely natural history of the tumor and general health of the patient. Management strategies include surgery for cure or palliation, and a variety of other cytoreductive techniques, and medical treatment including chemotherapy, and biotherapy to control symptoms due to hormone release and tumor growth, with somatostatin analogues (SSAs) and alpha-interferon. New biological agents and somatostatin-tagged radionuclides are under investigation. Advances in the therapy and development of centers of excellence which coordinate multicenter studies, are needed to improve diagnosis, treatment and therefore survival of patients with GEP NETs.

Key words: Gastro-entero-pancreatic neuroendocrine tumors; Carcinoids; Entero-endocrine tumors; Pancreatic tumors; Medical treatment; Molecular targeted therapy

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INTRODUCTION

Neuroendocrine tumors (NETs) of the gastro-entero-pancreatic (GEP) system are rare and originate from the diffused endocrine system, located in the gastro-intestinal (GI) tract (carcinoids) and in the pancreas (insular tumors), with extremely varying clinical pictures. GEP NETs represent about 2% of all the GI tumors[1], but their prevalence has increased substantially over the past three decades, only in part as a consequence of increased awareness and improved diagnostic techniques[2]. The most recent estimates suggest a global clinical incidence of 2.5-5 cases/100 000 per year[2,3], with an autoptical incidence 2-5 times higher than the clinical one, and a slight predominance in females[4,5].

The term carcinoid (from the German *Karzinoide*) was introduced in 1907 by Oberndorfer to identify some ileal tumors, originating from the enterochromaffin cells (EC) that produce serotonin, characterized by a better prognosis in comparison with adenocarcinomas. Later the term was used to describe NETs, both of the gut and extra-intestinal sites (pancreas, lung and bronchus, liver, thymus), even though the term NET should always be used specifying the tumor's origin site, in order to avoid misunderstanding. The term carcinoid should be used to indicate the serotonin-secreting tumors[6].

The diffused endocrine system of the GEP tract is the widest of the whole organism, with at least 16 different types of endocrine cells that produce more than 50 peptides or amines[2,6,7]. GEP NETs arise within the GI tract, but NETs can also occur elsewhere such as in the bronchus and lung (bronchial epithelium), hypophysis, thyroid, parathyroids, thymus, adrenal cortex and medulla, and paraganglia. GEP NETs can preserve and amplify the activity of the origin cells

characterized by secretion of a number of peptides and neurotransmitters, which can lead to the development of typical clinical syndromes by the so called "functioning" tumors, or they can be biologically inactive ("non-functioning" tumors)[1,2,8] for several reasons (defect of hormonal synthesis/secretion, rapid hormone degradation, synthesis of precursors/inactive hormones, co-secretion of antagonist hormones).

GEP NETs are usually sporadic, but they may also be multiple and may occur in some genetic syndromes such as multiple endocrine neoplasia (MEN) type 1, von Hippel-Lindau syndrome, neurofibromatosis type 1 and tuberous sclerosis[2,9,10]. Their frequency in these syndromes varies from very low (< 1%) for carcinoid to high (80%-100%) for pancreatic endocrine tumors (insulinomas 5%-20%, gastrinomas 25%-30%, non-functioning > 50%)[6].

CLASSIFICATION

As GEP NETs represent a heterogeneous group of tumors, their classification is still a critical point. In the past, GEP NETs were classified according to their embryonic origin and, according to the classification of William and Sandler[11], three distinct groups have been identified: (1) carcinoids derived from the proximal GI tract (foregut), located in the stomach, proximal duodenum, biliary tract and pancreas fed by the celiac tripod; (2) carcinoids derived from intermediate GI tract (midgut), located in the distal duodenum, small intestine, appendix and right colon, fed from the superior mesenteric artery; (3) carcinoids of the distal intestine (hindgut) localized into the descending colon, sigmoid colon and rectum, fed from the inferior mesenteric artery.

The most recent WHO classification[12] (Table 1) categorized all GEP NETs on the basis of clinical-pathological criteria as follow: (1) well-differentiated endocrine tumors, with benign or uncertain behaviour; (2) well-differentiated endocrine carcinomas, with a low-grade malignant behaviour; (3) poorly differentiated endocrine carcinomas (small cells carcinomas), with a high-grade malignant behaviour; (4) mixed endocrine-exocrine carcinomas, with characteristics of both endocrine and exocrine tumors. Each category includes functioning and non-functioning tumors.

However this classification has prognostic limits and a suboptimal reproducibility among pathologists hence TNM classification is being developed for NETs[13,14]. Table 2 provides examples of TNM classification for pancreatic NETs and carcinoids.

CLINICAL FEATURES

Clinical manifestations of GEP NETs are very heterogeneous: indeed, they can either remain asymptomatic for years, or can occur with obstructive symptoms, such as abdominal pain, nausea, vomiting, cholestasis, or can present with metastases, found accidentally, or can occur with typical syndromes due to hormonal hypersecretion. In most cases, because of vagueness of symptoms, the diagnosis is delayed (3-10 years on average), with an increased risk of developing metastases.

Gastrointestinal NETs (carcinoids)

NETs of the small intestine according to the Surveillance, Epidemiology, and End Results (SEER) database have an incidence of 0.15-0.5 cases/100 000 per year[15]. They are usually asymptomatic or characterized by obstructive symptoms, due to the local fibrotic reaction or, rarely, to the mass itself, until liver metastases appear[6]. At this stage, the typical clinical picture is the carcinoid syndrome that occurs in 18% of patients with ileal carcinoid[2,16] and is characterized by flushing, diarrhea, abdominal pain; less frequent events are lacrimation, profuse sweating, telangiectasias, cardiac fibrosis, and cutaneous manifestations pellagra-like due to lack of niacin (Table 3). Carcinoid syndrome is caused by the release of serotonin, which is no longer metabolized in the liver, and other substances, such as tachykinins, prostaglandins, and bradykinins[2,17].

Gastric carcinoids, that account for 4.6% of all carcinoids[15], originate from gastric EC-like mucosal cells, are mostly asymptomatic and occasionally found in the course of gastroscopies[6]; rarely they can cause an atypical carcinoid syndrome (flushing of greater duration than typical, of a red colour, with scialorrea, sweating, tearing, hypotension and itching)[16-18]. These carcinoids are divided into 3 groups: those that occur in chronic hypergastrinemic conditions, such as the type 1, associated with chronic atrophic gastritis, and type 2, associated with Zollinger Ellison syndrome in MEN-1, while type 3 is not associated with hypergastrinemia and is frequently malignant, with distant metastases.

Appendiceal endocrine tumors are often small and are found incidentally during appendectomies, with a frequency of 3-9/1.000 appendectomies and are usually benign[6,19-21]. Colonic carcinoids account for 8.6% of all carcinoids. They are often large and, among the intestinal carcinoids, have the worst prognosis[6,22].

Rectal carcinoids may present as an incidental finding on sigmoidoscopy or colonoscopy (1:2.500). They are typically small, non-functioning and distant metastases are rarely present at diagnosis (probably due to the early diagnosis)[6,22].

Carcinoids have previously been reported to be associated with secondary non-carcinoid malignancies, with rates as high as 46%-55%, more frequently located in the lung, breast, prostate and colon[23,24].

Pancreatic NETs

Endocrine tumors of the pancreas can occur with typical syndromes due to hormonal hypersecretion, such as insulinoma, gastrinoma, VIP-oma, glucagonoma and somatostatinoma (Table 4), but in a percentage of 40%-50% they are non-functioning or secrete peptide with a low biological impact, such as pancreatic polypeptide (PP) and neurotensin. Moreover a metastatic disease can be present at the time of diagnosis in approximately 50% of the cases[1,2,6,8].

Table 1 WHO classification[12]

Site	Well differentiated endocrine tumor		Well-differentiated endocrine carcinoma	Poorly-differentiated endocrine carcinoma
	BB	UB		
Pancreas	< 2 cm	⩾ 2 cm	Local invasion	Small cells
	< 2 mitoses[1]	> 2 mitoses	2-10 mitoses	> 10 mitoses
	< 2% Ki-67	> 2% Ki-67	> 5% Ki-67	> 15% Ki-67
	No vascular invasion	Vascular invasion	Vascular invasion ± metastases	Vascular/perineural invasion
Stomach	Mucosa/Submucosa	Mucosa/Submucosa	Invasion of muscularis propria ± metastases	Small cells
	⩽ 1 cm	> 1 cm		
	No vascular invasion	Vascular invasion		
Duodenum/	Mucosa/Submucosa	Mucosa/Submucosa	Invasion of muscularis propria ± metastases	Small cells
Jejunum	⩽ 1 cm	> 1 cm		
	No vascular invasion	Vascular invasion		
Ileum/	Mucosa/Submucosa	Mucosa/Submucosa	Invasion of muscularis propria ± metastases	Small cells
Colon/	⩽ 1 cm (ileum)	> 1 cm (ileum)		
Rectum	⩽ 2 cm (colon)	> 2 cm (colon)		
	No vascular invasion	Vascular invasion		
Appendix	⩽ 2 cm	> 2 cm	Extensive invasion of mesoappendix ± metastases	Small cells
	No vascular invasion	Vascular invasion		

[1]Mitoses expressed as number/10 high power field. BB: Benign behavior; UB: Uncertain behavior.

Table 2 TNM staging for pancreatic NETs[13], foregut and midgut gastrointestinal carcinoids[14]

	Pancreatic NETs			Foregut and midgut gastrointestinal carcinoids		
T-primary tumor						
Tx	Primary tumor cannot be assessed			Primary tumor cannot be assessed		
T0	No evidence of primary tumor			No evidence of primary tumor		
T1	Tumor limited to the pancreas and size < 2 cm			Tumor invades mucosa or submucosa and size ⩽ 1 cm		
T2	Tumor limited to the pancreas and size 2-4 cm			Tumor invades muscularis propria and size > 1 cm		
T3	Tumor limited to the pancreas and size > 4 cm or invading duodenum or bile duct			Tumor invades subserosa		
T4	Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or superior mesenteric artery)			Tumor invades adjacent structures		
	For any T, add (m) for multiple tumors			For any T, add (m) for multiple tumors		
N-regional lymph nodes						
Nx	Regional lymph nodes cannot be assessed			Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastases			No regional lymph node metastases		
N1	Regional lymph node metastases			Regional lymph node metastases		
M- distant metastases						
Mx	Distant metastases cannot be assessed			Distant metastases cannot be assessed		
M0	No distant metastases			No distant metastases		
M1	Distant metastases			Distant metastases		
Disease stage						
Ⅰ	T1	N0	M0	T1	N0	M0
Ⅱa	T2	N0	M0	T2	N0	M0
Ⅱb	T3	N0	M0	T3	N0	M0
Ⅲa	T4	N0	M0	T4	N0	M0
Ⅲb	Any T	N1	M0	Any T	N1	M0
Ⅳ	Any T	Any N	M1	Any T	Any N	M1

Criteria for carcinoids of the appendix and colon rectum differ only for the tumor size.

Insulinoma and gastrinoma are the most frequent pancreatic NETs. The incidence of insulinomas is 2-4 new cases/1 000 000 per year, whereas that of gastrinoma is 0.5-4 new cases/1 000 000 per year[8,25].

Insulinoma are usually (90%) benign tumors, most are small (> 90% are < 2 cm) and single, 6%-13% are multiple, and 4%-6% are associated with MEN-1. Clinically they are characterized by fasting hypoglycemia and neuroglycopenic symptoms. Moreover the release of catecholamines induced by hypoglycemia produces symptoms such as sweating, tremor and palpitation. Diagnostic procedures are given in Table 4.

Gastrinoma is a NET secreting gastrin. The chronic hypergastrinemia results in marked gastric acid hypersecretion that ultimately causes peptic ulcer disease, often refractory and severe, diarrhea and gastroesophageal reflux disease (Zollinger Ellison Syndrome, ZES).

At the time of diagnosis 50%-60% of gastrinomas are malignant. The tumor is preferentially located in the pancreas (24%-53%) and in the duodenum (13%-49%). Approximately 20% of gastrinomas are part of MEN-1. The diagnosis requires the demonstration of hypergastrinemia with hyperchlorhydria (Table 4).

Table 3 Carcinoid syndrome

Clinical features	Incidence (%)	Characteristics	Mediators
Flushing	90	Foregut tumors: prolonged fit, red-purple, localized to face and trunk. Midgut tumors: quick fit, pink-red.	Serotonin, histamine, P substance, prostaglandins
Diarrhea	70	Secretory	Serotonin, histamine, VIP, prostaglandins, gastrin
Abdominal pain	40	Long lasting	Obstruction, hepatomegaly, intestinal ischemia, fibrosis
Profuse sweating	15		Serotonin, histamine
Telangiectasias	25	Face	Unknown cause
Heart disease	30 (right)	Valvulopathies (tricuspid valve, pulmonary valve). Right heart failure. Dyspnea	P substance, serotonin
	10 (left)		
Pellagra	5	Dermatitis	Deficit of niacin

Table 4 Clinical features of the main endocrine pancreatic tumors

Tumor (syndrome)	Clinical features and diagnostic tests	MEN-1 (%)	Metastases (%)	SnSRS (%)
Insulinoma	Spontaneous or fasting hypoglycemia (Whipple's triad) Positive fasting test (hypoglycemia with hyperinsulinism)	8-10	10	50
Gastrinoma (Zollinger-Ellison syndrome)	Peptic ulcers, diarrhea, GERD, BAO > 15 mEq/h Positive secretin test (serum gastrinemia > 200 ng/L within 10 min from secretin venous infusion, 2 U/kg per min)	30	60	80
VIP-oma (Verner Morrison syndrome)	Severe watery diarrhea (> 1L/die), hypokalemia, hypochlorhydria	Rare	70	80
Glucagonoma	Necrolytic migratory erythema, diabetes, weight loss, anemia, hypoaminoacidemia, venous thrombosis	Rare	60	80
Somatostatinoma	Diarrhea, steatorrhea, weight loss, diabetes, cholelithiasis	Not associated	84	80
CRH/ACTH-oma	Cushing's syndrome	-	90	-
GHRH-oma	Acromegaly	-	-	-

SnSRS: Sensitivity of ^{111}In-Pentetreotide scintigraphy (Octreoscan®).

VIP-omas are NET that secretes VIP, which causes a distinct syndrome (Verner Morrison syndrome) characterized by large volume watery diarrhea, hypokalemia and dehydration. Pancreatic VIP-omas are rare (3%-8% of all pancreatic NETS)[8,25]. They are usually large (72% are > 5 cm) and malignant at the time of diagnosis (64%-92%). Extra-pancreatic VIP-omas may occur in pediatric patients and are neurogenic tumors (ganglioneuromas, ganglioneuroblastomas, neuroblastomas and pheochromocytomas).

Glucagonomas are rare (1/20 000 000 per year)[8,25,26]. They are usually large tumors at diagnosis with a size of 5-10 cm and from 50% to 82% are metastatic. The most common presenting feature is necrolytic migratory erythema, associated with glucose intolerance or diabetes, anemia, weight loss, depression, diarrhea and thromboembolism.

Somatostatinomas are rare tumors of either the pancreas or the upper small intestine, usually duodenum, near the ampulla of Vater. Somatosatinomas can be part of neurofibromatosis 1. Pancreatic tumors are usually large and metastatic (70%-92%) at diagnosis. The clinical symptoms include: diabetes, cholelithiasis, diarrhea with steatorrhea, hypochlorhydria, abdominal pain, weight loss and anemia.

Other rare tumors include CRH/ACTH-omas, GRF-omas, calcitoninomas and neurotensinomas[26]. Non functioning tumors constitute 30%-50% of all pancreatic NETs and differentiation from pancreatic adenocarcinomas is extremely important because prognosis is clearly different. The tumors are usually large, can be multifocal when are part of MEN-1 and malignancy rate varies from 62% to 92%[25].

DIAGNOSIS

Hormonal dosages

Several circulating or urinary tumor markers can be used for the diagnosis and follow-up of GEP NETs.

Among the generic markers, chromogranin A (CgA), a glycoprotein contained in secretion granules of neuroendocrine cells, has become the most important circulating tumor marker for the diagnosis and follow-up of NETs[27,28]. Elevated circulating levels of CgA are found in about 60%-80% of GEP NETs, both functioning and non-functioning[29], even if other non-neoplastic conditions, such as renal insufficiency, atrophic chronic gastritis, therapy with proton pump inhibitors[30,31] can determine false-positive results, reducing its specificity. Other generic markers include neuron-specific enolase (NSE), PP and human chorionic gonadotropin, with lower diagnostic accuracy than CgA[6,32].

5-hydroxyindoleacetic acid (5-HIAA) is the specific marker for carcinoids producing serotonin[2,6,18,32]; it is a metabolite of serotonin that can be determined in 24 h urines. The sensibility of the urinary 5-HIAA is about 65%-75%, while its specificity between 90%-100%[6].

Certain foods and drugs will affect the urinary excretion of 5-HIAA if they are taken in the 3-5 d before collection

of the urine sample. Bananas, avocados, aubergines, pineapples, plums, walnuts, cough syrup, paracetamol, fluorouracil, methysergide, levodopa, aspirin, 5-aminosalicylic acid (5-ASA), naproxen and caffeine may cause false-positive results. Adrenocorticotrophic hormone (ACTH), glucocorticoids, heparin, isoniazid, methyldopa and phenothiazines may give false-negative results[6].

For functioning NETs, the dosage of the specific hormone that causes the characteristic syndrome represents the specific tumor marker[1,6,8]. In particular in patients with suspected insulinoma, glycemia, insulin, peptide C and pro-insulin must be tested. Further biochemical tests include the prolonged fast (48-72 h), which is the gold standard for establishing the diagnosis of insulinoma. Indeed, 98% of patients with insulinoma will develop symptomatic hypoglycemia within 72 h.

In Zollinger Ellison syndrome, serum gastrin and basal gastric acid output should be evaluated[33,34]. If the gastrin is $\geqslant$ 1000 ng/L and gastric pH $<$ 2.5, the diagnosis is established. The secretin test is the provocative test of choice in patients with gastrin levels $<$ 1000 ng/L (Table 4). Plasma vasointestinal polypeptide (VIP) determination is used to diagnose VIP-oma in the suspicion of Verner-Morrison syndrome, plasma glucagon for glucagonoma, and serum somatostatin for somatostatinoma[1,6,8].

Imaging

Different integrated techniques can be used for diagnosis[1,2,6,35]. Imaging has an important role in localizing the primary tumor, identifying sites of metastatic disease and assessing response to treatment. The gastric and intestinal tumors are usually well studied with endoscopic techniques and endoscopic ultrasound. The tumors of the small intestine may require, besides enforcement of traditional radiological techniques (small bowel barium studies), the use of the most current techniques for studying small bowel (double balloon enteroscopy, video endoscopic capsule). Both for carcinoid and pancreatic tumors, computer tomograghy (CT) and magnetic resonance imaging (MRI) are important in defining the extent of metastatic disease and assessing response to treatment. Both techniques appear to have similar sensitivities for detection of these tumors, ranging from 30% to 94%[35]. Endoscopic ultrasound has an important role in the preoperative assessment of the pancreas where a small functioning tumor or the possibility of multiple tumors is suspected. This technique is very successful in expert hands, with sensitivities as high as 79%-100% being reported[35].

Functional imaging modalities, such as somatostatin receptor scintigraphy (SRS, Octreoscan®), have great impact on patient management by providing tools for better staging of the disease, visualization of occult tumor, and evaluation of eligibility for somatostatin analogue (SSA) treatment. In fact NETs generally express somatostatin receptors and by administering a radiolabelled SSA, the tumor is highlighted by the scintigraphic investigation. The SRS is a highly specific examination with sensitivity, for tumors of more than 1 cm, approximately of 80%-90% (with the exception of insulinoma that expresses somatostatin receptors in only 50% of cases)[1,2,6,36,37]. SRS also detects distant metastases with a sensitivity that can reach 96%[2,6]. It should be also noted that a positive SRS may lead to a possible systemic SSAs treatment or radionuclide therapy. On the other hand, even more sensitive techniques are being developed, based on methods combining PET-CT using [^{18}F] levodopa, 5HTP [^{11}C] or [^{68}Ga] linked to a SSA (^{68}Ga-DOTA-octreotide-PET)[36].

On the contrary, PET with conventional fluoro-deoxy-glucose has not proven advantageous for NET imaging, because of GEP NETs' low metabolic activity, with the exception of tumors with high proliferative activity and low differentiation[36].

Finally angiographic techniques, with the possible establishment of hormonal gradients, are currently used only in special cases and adequately equipped centers.

Pathology

Histopathological examination is the main criterion of the WHO classification[12] (Table 1), which takes into account: tumor size, number of mitosis, presence of cellular atypias, proliferative index, angioinvasion. Immunohistochemistry is also one of the most important techniques for the study of NETs. Several antibodies are available both against general endocrine markers such as NSE, synaptophysin and CgA, and against specific hormones.

It is also important to discriminate well-differentiated forms from poorly-differentiated carcinomas using malignancy markers. With this aim, the immunohistochemical expression of Ki67 seems as important as the determination of the mitotic index, expressed as the number of mitoses/10 high power fields[6,38].

TREATMENT

Surgical treatment

If possible, radical surgery is the cornerstone of the treatment of primitive GEP NETs. If there is loco-regional or liver metastases a debulking surgery can be performed in patients in whom 90% of the tumor is removable. It is suggested to perform a palliative surgery in the following clinical situations: (1) on the primary tumor with non-operable liver metastases (particularly in functioning tumors) because symptoms correlate with neoplastic mass; (2) if the primary tumor is localized in the small bowel, as it can lead to bowel obstruction; (3) in the case whereby surgery allow a subsequent multimodal treatment.

A combination of several therapies can be performed for liver metastases, such as surgical resection, (chemo) embolization, radiofrequency ablation and, in selected cases, orthotopic liver transplantation may be considered[16,39,40]. Although there are few studies that compare different treatment options on liver metastases, it would seem that different treatments improve survival

Table 5 Results of studies of molecularly targeted agents in patients with neuroendocrine tumours[54,55]

Agent	Response rate (%)	PFS rate (%)/Duration
VEGF monoclonal antibody		
Bevacizumab[56]	18	95 at 18 wk
mTOR inhibitor		
RAD001 (everolimus)	13	71 at 24 wk
Temsirolimus[57]	5.6	50 at 6 mo
VEGF TKI		
Sunitinib	10	Median, 42 wk
Vatalanib	In progress	(time to progression)
Sorafenib	In progress	
Pazopanib	In progress	
PDGFR/Kit/Abl inhibitor		
Imatinib[58]	4	Median, 5.9 mo
EGFR inhibitor		
Gefitinib	4	61 (carcinoids) and 31 (pancreatic tumor) at 6 mo
Other		
Bortezomib[59]	0	Median, 3 mo (Time to treatment failure)

PFS: Progression free survival.

rate at 5 years globally from 30% for the untreated tumor to 50%-70%[39,40].

Medical therapy

Medical treatment of NETs is different depending on whether the tumor is a well-differentiated or a poorly differentiated one. Functioning tumors are usually well differentiated and the first target of therapy is the control of symptoms. As these tumors are generally slow in growth, with a relatively long life expectancy, it is essential to ensure patients a good quality of life.

Treatment of gastrinomas is based on the use of proton pump inhibitors at an appropriate dosage (omeprazole and lansoprazole 40-60 up to 120 mg/d)[41,42]. Insulinomas are treated with diazoxide associated with hydrochlorothiazide; if this therapy is ineffective calcium channel blockers, beta blockers and glucocorticoids can be used[43]. For other well-differentiated cancers therapy is based on the use of SSAs, interferon and, more recently, targeted therapy[44,45].

Somatostatin is a hormone that inhibits the secretion of various hormones and peptides; somatostatin receptors are present in most well-differentiated GEP NETs (70%-95% of tumors), with the exception of insulinoma. SSAs allow control of hormonal-related symptoms and should be used both in a preoperative setting and in inoperable tumors[44]. They are sometimes used as antiproliferative agents, even if clinical studies have given disappointing results with regard to tumor regression and tumor shrinkage is demonstrated in less than 10% of the patients at standard dosage, although about 50% of patients can show stabilization of tumor size[46]. A possible positive effect on tumor volume regression with high-dose SSAs has yet to be demonstrated. Two different SSAs, octreotide and lanreotide, are used clinically. These analogues bind principally to the receptor subtypes 2 and 5. Recently pasireotide, a somatostatin analog with high affinity for all types of somatostatin receptors, has been introduced and has been shown to be effective in patients who do not respond to the currently available SSAs octreotide and lanreotide[47]. However, its use is still restricted to clinical studies. Altogether, SSAs are safe, easy to use, and well tolerated by patients experiencing only mild and infrequent side effects, among which are diarrhea, abdominal pain, steatorrhea, and cholelithiasis[48].

In addition, alpha interferon, such as monotherapy or in combination with SSAs, can be used to inhibit hormone hypersecretion and to stabilize the disease, with variable response rates. There has been biochemical response in 40%-60% of patients, symptomatic improvement in 40%-70% of patients, and significant tumor shrinkage in a median of 10%-15% of patients[48,49]. Interferon is used for the same indications as are SSAs in NETs of the gut, except for carcinoid crisis. Side-effects are generally mild, flu-like syndrome, fatigue, weight loss, polyneuropathy, myositis, thrombocytopenia, anemia, leukopenia, hepatotoxicity and neutralizing antibodies.

Poorly differentiated tumors are generally treated with different chemotherapy schedules. The role of chemotherapy in the treatment of GEP NETs is still uncertain, as variable response rates in different studies have been reported. While well-differentiated tumors are not responsive to chemotherapy (based on streptozotocin, doxorubicin, dacarbazine and 5-flurouracile variously associated with each other)[6,50] with only about 10% of carcinoids having a positive response, the best response rates (40%-70%) have been reported in some studies for anaplastic cancer, using different schemes based on cisplatin and etoposide, although there is no unequivocal evidence of survival improvement[51-53]. Furthermore, randomized controlled trials on chemotherapy *versus* biological treatment (SSAs with/without interferon) are still lacking.

GEP NETs can over express some molecules, such as epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF) and its receptor (VEGFR) or insulin-like growth factor receptor (IGFR), that can be targeted by some new drugs under assessment in early clinical trial (see Table 5)[54-59]. Other molecular therapies currently under investigation include the Raf-kinase inhibitor sorafenib and the inhibitor of the mTOR pathway, everolimus (RAD001)[54,55].

Peptide receptor radionuclide therapy (PRRT)

Another therapeutic approach is PRRT, which uses somatostatin analogs to convey radioactivity within the tumor itself (using generally ^{90}Ittrium, ^{177}Lutetium or ^{111}Indium), through somatostatin receptors[60,61]. PRRT can be considered in patients with inoperable GEP NETs and positive nuclear medicine imaging. According to some studies a stabilization of the disease can be reached in 50%-70% of cases[62-64] and control of symptoms in 70%[60]. Data in the literature, which however are not based on randomized, comparative studies, seem to favor [^{177}Lu-DOTA, Tyr] octreotate as

the most suitable peptide and radionuclide for PRRT[65]. Currently, tolerated dose is defined by the dose tolerated by the critical organs, kidney and bone marrow; it is likely that the dose can be modified in the future by more sophisticated, individually tailored dosimetry models, and by the introduction of new protective agents, different treatment schedules and radionuclides. This treatment has to be carried out in centers properly equipped and is to be reserved for selected cases.

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