Treatment of NET-Related Symptoms

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Abbreviations

ACTH	Adrenocorticotropic hormone
BM	Bowel movements
CC	Carcinoid crisis
CHD	Carcinoid heart disease
CS	Carcinoid syndrome
GH	Growth hormone
GHRH	Growth hormone-releasing hormone
IFN-alpha	Interferon-alpha
LAR	Long-acting release
NETs	Neuroendocrine tumors
pNET	Pancreatic neuroendocrine tumors
PPI	Proton pump inhibitors
PRRT	Peptide receptor-targeted radionuclide therapy
PTH	Parathyroid hormone
PTHrP	PTH-related peptide
SA	Somatostatin analogs
u5-HIAA	24-hour urinary 5-hydroxyindoleacetic acid
ZES	Zollinger–Ellison syndrome

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7.1 Introduction

Generally, a delay of 53.8 months occurs in the diagnosis of neuroendocrine tumors (NETs) [1, 2], and patients with functioning NETs have a shorter overall survival than those with nonfunctioning NETs [3]. Beside overall survival and comorbidities, hormonal syndrome can also be related to quality of life, as for example, in the case of increased frequency of bowel movements (BM) in carcinoid syndrome CS [4]. For these reasons, timely diagnosis and proper treatment for syndrome control are crucial for patients with functioning NETs. This chapter will deal with the treatment of functioning NETs-related symptoms.

For the treatment of symptoms due to mass effects and for treatments aiming to reduce tumor burden in order to reduce hormonal secretion, see chapters on surgical procedures, locoregional treatments, and chemotherapy. Primary tumor resection in functioning NETs is controversial. There are data in the literature on improved survival after primary tumor resection of well-differentiated NETs metastatic to the liver [5]. Accordingly, some studies have demonstrated that this practice could help disease control [6–10] but data on survival improvement are scanty and hampered by many bias such as retrospective design of the studies [5]. Primary tumor resection should be carefully evaluated in a multidisciplinary team for patients with functioning NETs

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in order to reduce hormonal secretion (e.g., Zollinger–Ellison syndrome (ZES) patients, CS, insulinoma).

7.2 Carcinoid Syndrome

Carcinoid syndrome occurs in almost 20% of patients with well-differentiated NETs of the small bowel [11]. It usually presents with liver metastasis at diagnosis [11] and is rarely associated with NETs of other organs (pancreas, rectum, etc.) [12, 13]. CS can present as typical or atypical. In the first case (95% of cases), it is due to a huge production and release of serotonin and is characterized by diarrhea, abdominal pain, and flushing, [14] while atypical CS (5% of cases) is usually mediated by histamine and is characterized by prolonged flushing, ocular edema and hyperemia, bronchospasm, and hypotension [14]. Other substances such as tachykinins, prostaglandins, and callicrein can be secreted as biochemical mediators of CS.

Somatostatin analogs (SA) and especially long-acting SA remain the mainstay of CS treatment. Lanreotide and octreotide, the two agents commercially available, are equally effective for symptom control [15]. Literature provides us evidence of their antisecretory and antiproliferative effects [16, 17] along with a high tolerability [18]. Pasireotide, a multireceptor-targeted somatostatin analog that at the moment is not approved for NET treatment, has also been studied in patients with CS resistant or refractory to treatment with octreotide long-acting release (LAR) [19] showing symptom improvement. However, it was not superior to octreotide in a comparative trial [20]. In case of refractory CS, dose escalation above the upper labeled dosages should be considered [15, 21, 22], and successively, in case of persistence of symptoms, subcutaneous short-acting SA can be associated.

Interferon-alpha (IFN-alpha) is recommended as a second-line therapy in functionally active NETs [15]. It is recommended as an add-on therapy to SA. However, we should always keep in mind unfavorable side effects (especially flu-like symptoms, fatigue, thyroid dysfunctions) of INF-alpha while treating patients with it. A pegylated formulation with weekly administration can reduce side effects [23].

Telotristat is an oral inhibitor of peripheral serotonin synthesis, which acts by inhibiting tryptophan hydroxylase, the enzyme involved in the conversion of tryptophan to serotonin [24]. It may offer new possibilities for patients with refractory CS. In two prospective randomized clinical trials, telotristat demonstrated efficacy in reducing BM frequency and 24-hour urinary 5-hydroxyindoleacetic acid (u5-HIAA), and it also gave relief of symptoms during the assessment period [24, 25]. The percentage reduction of BM was greater in patients with greater percentage reduction of u5-HIAA. The clinical responses observed in these patients suggest that the assumption that diarrhea was mediated by serotonin and its reduction could improve symptoms was correct. Furthermore, telotristat etiprate was generally well tolerated, and there were no reports of depression and constipation [25] as reported previously for another tryptophan hydroxylase inhibitor [26]. Clinical trials that focused on telotristat safety showed a favorable safety profile and suggested that the depression observed [27, 28] could be related to the underlying disease or other causes recommending monitoring of patient's mood. Actually, it seems that telotristat does not cross the blood–brain barrier [29]. *Peptide receptor-targeted radionuclide therapy* (PRRT) with radiolabeled somatostatin analogs is an effective therapeutic option in patients with NETs [30]. PRRT usually involves administration of radiolabeled hormone analogs with high specificity to somatostatin receptors on tumor cells, leading to the internalization of the radioactivity into the tumor cells and consequent cell death [3]. The two most commonly used radiopeptides are ^{177}Lu-DOTATAE and ^{90}Y-DOTATOC [31, 32]. Netter-1 trial showed that PRRT is highly effective in controlling advanced progressive NETs along with a favorable safety and quality of life profile [33]. FDA

and EMA approval for the use of LutaThera™ in NETs will lead to increased use of PRRT in many countries. Patients with decompensated heart failure are not suitable candidates for PRRT, because it requires concomitant amino acid and fluid infusions before and along with peptide receptor radionuclide therapy [34].

Carcinoid heart disease (CHD) is a major cause of morbidity and mortality in patients with CS [34, 35]. Most frequently, it involves the pulmonary and tricuspid valves [35]. NT-proBNP for screening patients with carcinoid syndrome for evidence of clinically significant carcinoid heart disease and measurement of either 24-h urine 5-HIAA or plasma 5-HIAA are essential for diagnosis and follow-up of CS and CHD [34]. Furthermore, a 24-h u5-HIAA level >300 mmol/24 h seems to be a useful marker for identifying patients at risk for developing carcinoid heart disease [34]. Echocardiography and echocardiographic features seem to be the best modality in the evaluation of carcinoid heart disease and in the assessment of disease severity [34]. Cardiac magnetic resonance (CMR) and computed tomography (CT) scanning can be a valuable adjunct in the investigation of patients with CHD, especially where echocardiographic windows are poor or structures are difficult to visualize [36]. Patients with CHD and severe regurgitation should be referred for surgery, and the choice of valve prosthesis should be individually tailored [36]. An experienced medical (cardiologist, endocrinologist, oncologist), surgical and anesthetic team approach is mandatory for these patients in order to give them the best and complete management [34].

Carcinoid crisis (CC) is a life-threatening form of CS that occurs due to systemic release of a large surge of bioactive amines and peptides [3]. The classical (typical) CS is characterized by diarrhea, flushing, wheezing and shortness of breath, sudden changes in blood pressure, and hyperthermia [37]. CC can be precipitated by different conditions such as surgery, biopsies, PRRT, locoregional treatments, anesthesia, some kind of food, emotional stress, pain stimuli, certain medications, and alcohol intake. Some studies have identified patients with large tumor burden, already known CS, elevated chromogranin A and/or high 24-h u5-HIAA levels or preexisting CHD as high-risk patients for CC [3]. Other factors include increasing age, hepatic metastasis, previous exposure to octreotide, and increasing duration of anesthesia, but patients without these conditions can also develop intraoperative crises [38, 39]. PRRT is a procedure that increases the risk for hormonal crises [40], probably due to tumor lysis. According to the ENETS guidelines, long-acting SA should be discontinued 4–6 weeks before PRRT [41], while short-acting formulations can be given [41].

Electrolyte, vitamin, and protein abnormalities in CS patients should be corrected before surgery along with dehydration [42, 43]. Patients with severe diarrhea may require parenteral nutrition [44]. Patients with CHD who need to undergo surgery or other invasive procedures should also undergo preoperative evaluation by an expert cardiologist in CHD [44] to prevent low cardiac output syndrome due to right ventricular failure [44]. Various octreotide administration regimen and various schemes have been proposed [44]. Some authors suggest subcutaneous administration for low-risk patients and minor procedures [45], but intravenous octreotide infusions should be readily available since CC can be induced even by minor surgical procedures [44]. However, the intravenous administration is currently considered the most preferable one [46]. If patients already receive long-acting SA, they should be continued [44]. Some data in the literature suggest that patients pretreated with SA may require higher doses of octreotide infusion [46]. Most experts initiate prophylactic treatment with intravenous octreotide 12 h before surgery and escalate the dose as necessary to control symptoms at least 48 h after the operation [44]. It seems that intravenous octreotide at a starting dose of 50–100 microgr/h (mean dose 100–200 microgr/h) is currently used by most centers [42–44]. In addition, ondansetron may help for diarrhea control [47].

Patients with tumors originating from the foregut (especially lung, stomach, and duodenum) may present a less common atypical CS. Atypical SC is usually mediated by both histamine and serotonin and is characterized by patchy, intensely red flush, sweating, itching, cutaneous edema, bronchoconstriction, salivary gland swelling, lacrimation, and cardiovascular instability (mainly hypotension). In these patients, histamine urinary metabolite methylimidazole acetic acid must be controlled since 24-h u5-HIAA may be not elevated because of decarboxylation deficit [44]. In these patients, addition of H_1 receptor blockers and H_2 blockers is recommended, and sometimes also cortisone can be administered to block histamine peripheral actions [48, 49].

Specific recommendations about anesthesia and the drugs to prefer should also be considered in the management of CS patients. Appropriate pain relief and anxiety control can reduce catecholamines-mediated stress response, and this is very important since catecholamines are thought to contribute to the release of tumor products [42, 43, 50].

7.3 Hypoglycemia

Insulinomas are rare functional pancreatic neuroendocrine tumors (pNET) [51–53]. Symptoms of hypoglycemia (adrenergic and neuroglycopenic) with concomitant documented low blood glucose levels and the relief of symptoms by intake of carbohydrates (Whipple's triad) are strongly suggestive for the presence of an insulinoma [54]. However, documented levels of hypoglycemia with concomitant blood insulin, C-peptide, proinsulin, and β-hydroxybutyrate levels during a supervised 72-h fasting test, considered the gold standard, are needed to confirm the diagnosis of insulinoma [51, 54, 55] as well as the absence of sulfonylurea in plasma and/or urine [52, 53] and the absence of insulin antibodies [56].

Surgical exploration is recommended in all insulinoma patients with or without MEN1, if non-resectable metastatic disease is not present [57]. A laparoscopic approach is usually recommended in patients with sporadic disease and with imaged tumors [58]. In patients with a localized insulinoma, who are not candidates for surgery, ablative therapy either endoscopically or percutaneously with radiological guidance should be considered [57]. Prior to surgery or locoregional treatments, in order to control hypoglycemia and to reduce the risk of hypoglycemic crises during the procedure, medical therapy is very important. Besides treating patients with diazoxide (first-line treatment for hypoglycemia), 30–50% of them also respond to SA [57], but they need to be carefully monitored, because some of them may get worse [59–65] since SA also inhibit the secretion of counterregulatory hormones. Everolimus can be used in refractory hypoglycemia due to malignant insulinoma [2, 57], while treatment with glucocorticoids can be used because it induces hyperglycemia by inhibiting insulin secretion and increasing insulin resistance [2]. PRRT, even though experience in malignant insulinoma is very limited [2], may be an effective treatment option for hormonal syndrome control and tumor burden reduction or stabilization [33, 66, 67]. Sunitinib and pasireotide were also shown to be effective [57, 68], even though the experience is limited. However, it is not known which is the best and most effective therapeutic sequence in patients with malignant insulinomas.

7.4 Zollinger–Ellison Syndrome

Inappropriately elevated fasting serum gastrin in the presence of hypergastrinemia when gastric acid secretion (gastric pH < 2) is present suggests the diagnosis of Zollinger–Ellison syndrome (ZES) [57]. Routine surgical exploration is still not generally recommended in MEN1/ZES patients with pNETs < 2 cm [57]. Patients with sporadic gastrinomas and without contraindications should undergo surgical exploration by a gastrinomas dedicated surgeon [69]. Peritumoral lymph nodes should be removed in order to be assessed for prognostic

purposes and to increase the cure rate [57]. Enucleation is the generally recommended surgical procedure; pancreaticduodenotomy is reserved for selected cases [70–75]. pNETs with preoperative vascular involvement or invasion should be evaluated by a team well versed in this kind of surgery [57].

Proton pump inhibitors (PPI) remain the mainstay of medical therapy for gastric acid secretion control [57]. Hypomagnesemia and vitamin B_{12} deficiency can develop during long-term treatment [76–82]. Some epidemiological studies have also found an increased incidence of bone fractures even though this finding was not confirmed in other studies [57]. The high somatostatin receptor expression in gastrinomas makes them highly responsive to SA and supports the use of such drugs to control tumor growth in patients not amenable to surgical cure. However, only limited data exist to support the use of SSAs in advanced gastrinomas [83].

7.5 Glucagonoma

Glucagonoma is an uncommon neuroendocrine tumor arising from pancreatic islet alpha cells [84]. Its clinical manifestations include necrolytic migratory erythema, glucose intolerance or diabetes mellitus, and importantly weight loss [44, 84]. SSA, antibiotics, and amino acid infusion may improve syndrome control and may help heal skin lesions [44]. These patients are at high risk for deep venous thrombosis and pulmonary embolism. For this reason, they should also receive thromboprophylaxis especially before surgical procedures. Locoregional treatments and medical systemic therapy may also be considered based on disease extension and grading surgery.

7.6 VIPoma

VIPoma is generally a pNET secreting vasoactive intestinal peptide (VIP) that causes a clinical syndrome characterized by severe secretory diarrhea, which leads to severe hypokalemia, loss of bicarbonate, metabolic acidosis, and dehydration [44]. Patients must be treated for this life-threatening condition by correcting electrolyte abnormalities and dehydration. SA remain the treatment of choice for rare functioning NETs [44, 57] prior to surgery or if resection is not possible.

7.7 Somatostatinoma

Somatostatinomas are NETs of the pancreas, duodenum, or jejunum [57], and, at present, there are more than 100 cases described in the literature [57]. The clinical syndrome is characterized by diabetes mellitus, cholelithiasis, diarrhea, and steatorrhea [57, 85]. Primary tumor and metastasis surgery, when possible, can help treat symptoms due to tumor load, hormonal secretion, and obstructive symptoms [85]. With this aim, locoregional therapies may also be considered.

7.8 Ectopic Syndromes

Nonfunctioning NETs can also become suddenly functional NETs, and usually this is a poor prognostic factor [2]. Syndrome control is important in order to reduce comorbidities associated to the syndrome and in order to prepare the patient for surgical or other invasive procedures.

7.8.1 Syndrome of Inappropriate Antidiuresis (SIAD)

NETs syndrome of inappropriate antidiuresis (SIAD) is usually caused by small-cell lung carcinoma, but other neuroendocrine neoplasias can cause SIAD too [86]. SIAD is characterized by euvolemic hypotonic hyponatremia due to the antidiuretic effect of inappropriate levels of antidiuretic hormone (ADH). [87]. Hyponatremia correction is very important since it is a life-threatening situation. In severe symptomatic hyponatremia, infusion of 3% NaCl saline as

boluses or as a continuous infusion should be administered [88]. Vaptans, nonpeptide vasopressin receptor antagonists, cause serum sodium increase by inducing aquaresis [88]. Treatment is usually started with 7.5–15 mg per day. Cases of secondary resistance to tolvaptan in paraneoplastic SIAD have been reported despite increasing doses of tolvaptan [87]. The authors think that this can be due to extraordinarily high levels of ADH, rather than adaptive mechanisms at receptor level. Loss of aquaretic effect in these patients can represent disease progression [87].

7.8.2 Acromegaly

The incidence of acromegaly due to a pituitary adenoma is three cases per one million persons per year, and the prevalence is about 60 cases per million [89]. In less than 1% of cases, acromegaly may develop because of ectopic secretion of growth hormone (GH)-releasing hormone (GHRH) [90–95] or, more rarely, GH secretion from a nonpituitary origin, mostly from a neuroendocrine tumor (NET) [96–98]. Usually, it is secondary to pNETs or bronchial carcinoids, but NETs from other origin can also cause ectopic acromegaly [57]. There are reported cases of ectopic acromegaly in a patient with pheochromocytoma [99], lymphoma [98], and paraganglioma [89].

Surgical resection of the primary tumor [89] should be considered whenever possible in order to control syndrome, and, if it is not possible, curative SA should be used for their antiproliferative effect and hormonal excess control. After SA treatment, in case of persistence of high hormonal levels, pegvisomant, a GH receptor antagonist, should also be considered. In case of unresectable tumor or extensive metastasis, other systemic therapies, locoregional treatments, and radiotherapy should also be evaluated for syndrome control according to the extent, grading, and biological characteristics of the neuroendocrine disease [89].

7.8.3 Cushing Syndrome

Ectopic adrenocorticotropic hormone (ACTH) secretion has been reported primarily in patients with lung NETs [44], but can also be encountered in patients with gastrointestinal tumors [100, 101]. Syndrome control, especially before surgical procedures, is very important since ectopic hypercortisolism can cause severe hypokalemia, hyperglycemia, and high thromboembolic risk arising very quickly.

Drugs aiming at controlling hypercortisolism can act at the tumor level (SA, cabergoline), at the adrenals (metyrapone, ketoconazole), or at the glucocorticoid receptor. These drugs can also be used in association. Attention must be paid with ketoconazole that can interfere with the metabolism of other drugs such as anticoagulants, antibiotics, and chemotherapeutics. Hypokalemia must be corrected since these patients can present with rapid onset and severe hypokalemia that can cause cardiac rhythm alterations. Glucose levels control is also of crucial importance. Furthermore, these patients can present frailty fractures secondary to hypercortisolism, especially vertebral fractures, and for this reason adequate vitamin D supplementation and eventually antiosteoporotic treatment (such as zoledronate) should be considered. Finally, if medical therapy does not control hypercortisolism, bilateral adrenalectomy should be carefully considered by a multidisciplinary team and with a dedicated surgeon.

7.8.4 Hypercalcemia (PTHrP and MEN1)

Ectopic hypercalcemia may be secondary to ectopic production of parathyroid hormone-related peptide (PTHrP) [44] or, less commonly, to ectopic production of parathyroid hormone (PTH) [102]. In patients with uncontrolled hormonal syndrome, debulking surgery and hepatic locoregional treatment must be considered [44] despite systemic pharmacotherapy for the

neoplasia. The mainstays of medical treatment in case of severe ectopic hypercalcemia are patient rehydration and treatment with bisphosphonates (zoledronate, pamidronate) or denosumab with the aim to reduce bone resorption [103]. Hydrocortisone can inhibit calcium absorption and reduce extra renal calcitriol [103]. Treatment with furosemide is controversial. Cinacalcet mimics high levels of calcium to reduce PTH levels [104]. In case of patients unresponsive to pharmacotherapy or in case of severe hypercalcemia with important kidney failure, hemodialysis must be considered.

Hypercalcemic primary hyperparathyroidism can present in patients with pNETs in MEN1 syndrome. Although the optimum timing has not been defined, surgery for subtotal parathyroidectomy or total parathyroidectomy is recommended [105]. Total parathyroidectomy with autotransplantation may be considered. Patient management should be done by a NETs multidisciplinary experienced team that should include an experienced endocrine surgeon. Conventional open bilateral exploration is recommended, while minimally invasive parathyroidectomy is usually not recommended because multiple glands are typically affected [105]. Concurrent transcervical profilactic thymectomy is also suggested at the time of surgery [105]. While waiting for parathyroidectomy, hypercalcemia can be treated with cinacalcet and/or bisphosphonates.

7.9 Conclusions

Clinical syndrome control is paramount for comorbidities, mortality, and quality of life control in functioning NET patients. Whenever possible, surgery of the primary and/or metastasis should be considered in order to reduce tumor burden and consequently hormonal secretion. Because of their antiproliferative and antisecretive effects, SA are the mainstay for many hormonal syndromes in NETs. However, further investigation is needed for the use of multiple SA receptor pasireotide in the treatment of NET-related syndromes. According to the type of hormonal secretion, other medical treatments should be used alone or in combination therapy with SA in order to control symptoms, and to prepare the patient for procedures such as surgery, locoregional treatments, and PRRT. We still have to deal with syndromes that we cannot control at all, such as refractory CS, hypoglycemia in malignant insulinomas, or severe ectopic hypercortisolism. In the first case, telotristat has provided very promising outcomes, while for malignant insulinomas usually combination therapy with different sequences is recommended. For these reasons and with the aim to offer our patients the best treatment currently available, a multidisciplinary team approach is always crucial for treatment and follow-up.

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