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Medical Treatment of Endocrine Gastroenteropancreatic Tumors

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Introduction

Neuroendocrine gastroenteropancreatic (GEP) tumors are rather rare neoplasms with an incidence of 1-2 cases per 100,000 people [1, 2, 3, 4]. They originate from any of the various cell types belonging to the neuroendocrine system. A general characteristic of GEP endocrine tumors is that the vast majority produce and secrete a multitude of peptide hormones and amines. Several syndromes can be associated with GEP endocrine tumors, caused by hyperproduction of a specific hormone, and usually liver metastases are pre sent in patients because of the malignancy of the tumors [5, 6, 7, 8, 9, 10]. The syndromes include: carcinoid syndrome [10], Zollinger-Ellison syndrome [6], the so-called "insulinoma syndrome" [5], "glucagonoma syndrome" [7], Verner-Morrison syndrome, which is brought about by high circulating levels of vasointestinal peptide (VIP) [8], and finally the "somatostatinoma syndrome" [9].
Otherwise, there are some endocrine tumors, usually located in the pancreas, that are not associated with signs or symptoms of hormone hypersecretion, and therefore they are called nonfunctioning.
Because of the rarity of these types of tumors, their possible episodic expression and the variable clinical symptoms, the patients are often diagnosed late in the advanced stages of the disease. In contrast to other metastasized tumors, the patients with gut and pancreatic neoplasms often survive for long periods due to the slow tumor progression; instances of survival greater than 10 years have been reported [11]. For these reasons, the patients with advanced metastatic disease should be treated aggressively with medical and surgical therapies aimed at reducing both symptoms and complications through strategies that reduce tumor bulk and block hormonal effects.
Neuroendocrine tumor treatment is aimed at reducing the tumor mass and inhibiting hormonal release. Therefore, a multimodal approach is necessary where different therapeutic means can be used synchronously or metachronously [12].

Therapeutic Options

The surgical approaches consist of:

- radical resection of the mass;
- debulking procedures;
- palliative surgery.

Medical treatment includes:

- chemotherapy;
- somatostatin analogs;
- alpha-interferon (alpha-INF) alone or associated with analogs;
- radiolabeled somatostatin analogs;
- chemoembolization.

Chemotherapy

In general, neuroendocrine tumors are not highly chemosensitive; this may be due to their generally low rate of mitosis which is the target of many cytotoxic drugs, and also to their biological properties [13]. In well-differentiated endocrine tumors, chemo-therapy must be used only when the disease is in progression and when other types of treatment have already been tried. Otherwise, in poorly differentiated tumors and in pancreatic ones, streptozotocin (STZ) and 5-FU or cisplatin (CDDP) and etoposide (VP-16) represent the therapy of choice [14]. Therefore, chemotherapy is not the therapy of choice in patients with GEP tumors. In fact, it is indicated only in progressive, highly proliferating tumors not treatable by other methods [15] irrespective of the localization of the primary tumor [14]. Some authors, in particular Bajetta *et al*. [16], have tested new active chemotherapy regimens; they have proposed a polychemotherapy regimen (5-FU, dacarbazine and epirubicin) in patients with progressive advanced neuroendocrine GEP tumors, with promising results.

Somatostatin Analogs

Somatostatin (SST) and its analogs inhibit the release of a variety of hormones and several intestinal peptides. Furthermore, it is known that they can exert an antiproliferative effect on endocrine tumors using at least two mechanisms: the inhibition of the release of peptides from the pituitary gland, the intestine and the pancreas, and the direct antagonism of growth factor effects on tumor cells. They exert their effect through somatostatin receptors (SSTRs); in particular, somatostatin 14, the natural compound, binds all five subclasses (SSTR 1-5), whereas octreotide and lanreotide bind mainly type 2 and 5 [17]. The antiproliferative effects seem to be mediated by receptor 2 and 5; these effects can be obtained also by using of high dose of SST analogs [12].
The formulations currently available on the market are listed below:

- octreotide: 0.2, 0.2, 0.5 mg s.c. daily;
- lanreotide: 30 mg i.m. every two weeks;
- long acting release octreotide (octreotide LAR): 10, 20, 30 mg i.m. monthly;
- lanreotide injectable solution: 60, 90, 120 mg i.m. monthly.

The s.c. octreotide is useful in testing the tolerability of somatostatin, in preventing carcinoid crisis during surgical procedures and in those cases in which the syndrome is not under control. The standard dose of s.c. octreotide is 150 µg every 8 hours but this dose can be increased up to 500 µg to achieve better control of the carcinoid syndrome. Otherwise the long acting release SST analogs require monthly i.m. administration [18].
With regard to side effects, abdominal pain, nausea and flatulence may occur at the beginning of treatment and diarrhea is often present. After long term treatment, asymptomatic gallbladder microlithiasis has been reported on ultrasound examination [18].
In a recent consensus report, Oberg *et al*. [18] underlined the fact that somatostatin analogs represent the therapy of first choice as concerning endocrine GEP tumors and they must be used when the Octreoscan is positive. Furthermore, SST analogs must be used when there is a syndrome related to the tumor and when the disease is in progress. The use of these drugs is also necessary in preventing a carcinoid crisis during surgery [18]. Still controversial is the use of SST analogs after debulking or ablative procedures, after radical surgery as adjuvant therapy and in asymptomatic patients with metastases. Furthermore, Oberg e*t al*. [18] considered several studies concerning the use of SST analogs and concluded that the stable disease was obtained in 36-70% of patients with GEP tumors whereas the objective response was rare (0-7%).

Alpha-INF and SST Analogs

The use of alpha-INF was introduced for the first time by Oberg [14]. Alpha-INF has an

antiproliferative effect and inhibits some hormones and growth factors and also inhibits angiogenesis [14].
Alpha-IFN has been combined with the somatostatin analogs, especially octreotide with a significant potentiation of the clinical effects. In a recent study by Fjallskog ML *et al*. [19], 16 patients with metastatic endocrine pancreatic tumors were studied. The combination of octreotide or lanreotide and interferon alpha at a median dose of 9-25 MU/week produced a biochemical response in 62.5% of the patients (median duration 22 months) and a radiological response in 19% (median duration 23 months) [19].
The most common side effects of alpha-INF are flu-like symptoms, weight loss, anemia, allergic reactions, vasculitis and hypo-thyroidism [14].
Some Authors have studied the association between alpha-INF and chemotherapy, 5-FU or STZ or doxorubicin, but this combination did not seem to present any advantages over alpha-INF alone and the side-effects were considerable [20, 21].

Chemoembolization

This treatment represents the therapy of choice when there are hepatic lesions due to a well-differentiated extra-pancreatic endocrine tumors [22]. Chemoembolization can be considered as complementary or alternative to chemotherapy or biotherapy when hepatic lesions are unresectable and when there are post-surgical relapses. The contraindications are: the involvement of hepatic parenchyma, more than 50%, renal failure, biliary anastomosis, ascites and portal thrombosis [11].
The drugs most frequently used are STZ, 5-FU and adriamycin which can be associated with lipiodol, while the most frequently used embolizing substance is gelfoam. The method carried out using, for the most part, adriamycin associated with spongel and sipiodol produced a control of the symptoms in 73-100% of patients with a decrease of the 5-hydroxyindolamine acetic acid (5-HIAA) which varies from 57 to 91%. Regarding tumor size (according to WHO criteria), the majority of authors have observed an objective response in about 50% of patients with duration of the response varying from 6 to 42.5 months [23, 24, 25, 26, 27].
Chemoembolization can be repeated at intervals of 3-6 months according to individual tolerability and tumoral response. The most frequent collateral effects are nausea, vomiting, abdominal pain, hyperpyrexia and an increase in transaminase levels which constitute the so-called post-chemoembolization syndrome. The most important complications are acute cholecystitis and hepatic and/or renal failure. In functioning tumors of the pancreas and in carcinoids, pre-medication with somatostatin in continuous infusion or with s.c octreotide. is indicated in order to prevent complications caused by the release of peptides and amines which is seen during necrosis of the neoplastic cells [12].
Therefore, chemoembolization could be an alternative treatment for progressive liver metastases, mainly following unsuccessful systemic chemotherapy. As concerns survival, currently there are no precise or definitive results therefore further studies on a larger number of patients are required.

Radiometabolic Therapy

In recent years some researchers have tried to develop a somatostatin analog which has a high affinity for somatostatin receptors and which could be linked to a therapeutic beta-emitting radioisotope. The crossfire of beta-particles can destroy both somatostatin receptor-positive and receptor-negative tumor cells Therefore, there is a new generation of SST analogs which ensure better stability of the radiometal-peptide complex incorporating the chelator DOTA and labelling with 90Y (DOTATOC) or 177Lu (DOTATATE) [28, 29, 30].
Many reports show the usefulness of peptide receptor radionuclide therapy (PRRT) in neuroendocrine functioning tumors [31, 32].

In a recent study by Kwekkeboom *et al*. [33] with 177Lu-octreotide,DOTA(0),tyrosyl(3) in patients with GEP tumors, it was found that this type of treatment obtains a partial response in 20-63% of the patients and a stable disease in 12-42%. Furthermore, serious side effects are rare and the results are better in patients with limited tumor load. Therefore, early treatment, even in patients who have stable disease, may be better [33].

Keywords Chemoembolization, Therapeutic; Endocrine Gland Neoplasms; Octreotide; Radioimmunotherapy

Abbreviations 5-HIAA: 5-hydroxyindolamine acetic acid; CDDP: cisplatin; GEP: gastroenteropancreatic; INF: interferon; octreotide LAR: long acting release octreotide; PRRT: peptide receptor radionuclide therapy; SST: somatostatin; SSTR: somatostatin receptor; STZ: streptozotocin; VP-16: etoposide

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