Neuroendocrine gastrointestinal tumors – a condensed overview of diagnosis and treatment

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Summary

Neuroendocrine gut and pancreatic tumors are rather rare malignant diseases which has gained increased attraction through the last decennium, possibly through development of new diagnostic and therapeutic methods. Histopathology demonstrating the common neuroendocrine features of these tumors has been the diagnostic cornerstone for long, but today it should be supplemented with information about the tumor biology. An excellent biochemical marker which is easy to analyze in serum or plasma is chromogranin A, which is a glycoprotein that is stored and released from neuroendocrine cells. This marker can be used for diagnosis and follow-up of the patients.

Somatostatin receptor scintigraphy has been one of the most important diagnostic tools for staging of the disease and also indicating sensitivity to treatment with somatostatin analogues. It is a general agreement that almost every patient should be subjected to this procedure before or during the treatment course.

From the therapeutic point of view, surgery is nowadays more extensive aiming at reducing the tumor mass in patients who could not be cured by surgery alone. Other means of tumor reduction is liver dearterialization by embolization with starch spheres.

The medical treatment of neuroendocrine tumors has made a real break through with the introduction of somatostatin analogues, particularly octreotide, and today most of the hormonally related symptoms can be controlled by this kind of treatment. Somatostatin analogues have also shown to be inhibitors of tumor growth and the latest development is tumor targeted radioactive treatment with Ytrium or Indium labelled octreotide. Long-acting formulation of somatostatin analogues have come into clinical use and significantly improved quality of life for patients with neuroendocrine tumors.

Other means of medical treatment are alpha interferons, which have shown particular effect in patients with midgut carcinoid tumors giving both biochemical and tumor responses. Chemotherapy such as streptozotocin plus 5-fluorouracil (5-FU) or doxorubicin is still considered as first-line treatment in malignant endocrine pancreatic tumors but is combined with concomitant somatostatin analogue treatment.

In the future a multimodal treatment will further develop combining different agents and also somatostatin receptor subtype specific analogues will come into clinical use.

Key words: α-interferon, chemotherapy, chromogranin A, octreotide, receptor scintigraphy, somatostatin, surgery

Introduction

Neuroendocrine gut and pancreatic tumors constitute about 2% of all malignant gastrointestinal neoplasms. The incidence of patients with malignant tumors and the carcinoid syndrome is around 0.5/100,000 and with pancreatic endocrine tumors 0.4/100,000. Many patients with malignant metastasizing tumors demonstrate clinical symptoms related to hormone overproduction. These include the carcinoid syndrome with flushing, diarrhoea, bronchial constriction and right heart failure, mainly from so called 'midgut' carcinoids producing serotonin and tachykinins. Syndromes related to pancreatic endocrine tumors are the Zollinger–Ellison syndrome from overproduction of gastrin and insulinoma causing hypoglycemia because of excessive production of insulin/proinsulin. Other distinct clinical entities are the glucagonoma syndrome with typical necrotic migratory erythema, the Verner–Morrison syndrome (WDHA-syndrome) from high circulating levels of VIP producing severe secretory diarrhoea with various degrees of electrolyte disturbances, and finally somatostatinoma leading to a syndrome of gall bladder dysfunction, gall stones, steatorrhea and impaired glucose tolerance [1, 2].

Carcinoid tumors are divided into three main groups; foregut, midgut and hindgut tumors. Primary foregut tumors are confined to the thymus, lung, gastric mucosa or duodenum (10%–15%), whereas midgut carcinoids are located predominantly in the distal part of ileum, caecum and proximal colon (50%–70%). Appendix carcinoids are benign and rarely give rise to metastatic disease. The hindgut tumor are primarily located in distal colon and rectum and they constitute the second most common type (15%–20%) of all carcinoids. The midgut carcinoids dominate the malignant carcinoid tumors, particularly when the carcinoid syndrome is present [3, 4].

About one-third of patients with pancreatic endocrine
A neuroendocrine tumor is suspected when classical clinical symptoms occur but might also be suspected when the patient present diffuse abdominal symptoms. The initial diagnosis is primarily biochemical and the most important screening marker today is chromogranin A (CgA) [6]. It is a glycoprotein present in almost all neuroendocrine cells and is elevated in about 80%-100% of patients with demonstrated neuroendocrine tumors. It is also found elevated in other neuroendocrine tumors such as pheochromocytomas, ganglioneuromas and neuroblastomas. Plasma CgA might then be supplemented with analysis for other 'general' markers such as pancreatic polypeptide and HCG-α and -β subunits. Specific markers for carcinoid tumors include urinary 5-HIAA, plasma neuropeptide K, neurokinin A and substance P and in cases with foregut carcinoid also serum gastrin, plasma somatostatin and ACTH. In patients with suspected endocrine pancreatic tumors, markers are selected according to clinical symptoms and might include serum, gastrin, pancreatic polypeptide, plasma somatostatin, VIP and glucagon. The value of different biochemical markers in carcinoid tumors is shown in Table 1.

**Localisation procedures**

Previously localisation procedures have included Barium enema, angiographies and pulmonary X-rays. Today the basic program includes CT-scan, MRI, ultrasound investigations and quite recently somatostatin receptor scintigraphy and positron emission tomography.

Different means of endoscopy is important in localising tumors, both gastroscopy and colonoscopy is important and quite recently endoscopic ultrasound has been quite successful to show small endocrine pancreatic tumors.

Today somatostatin receptor scintigraphy is the most important screening procedure for neuroendocrine gastrointestinal tumors [7, 8] (See the paper by Krenning et al. in the present supplement). Of course it should be supplemented by a CT-scan or MRI, necessary to follow during therapy. Ultrasonography is good to unveil liver metastases.

**Histology**

The final diagnosis should always be based on histopathology. The neuroendocrine features should be demonstrated by either a silver staining method (Grimelius staining) or immunohistochemistry for chromogranin A, synaptophysin or NSE. More specific diagnosis include immuno-histochemistry for serotonin, gastrin, glucagon, VIP and so forth. The proliferation marker Ki-67 (or PCNA) should be included to determine the growth potential of the tumor and selection of therapy (see the present paper by Solcia et al. in this supplement). The diagnostic work-up is summarized in Figure 1.

**Table 1. Tumor markers in 301 carcinoid patients.**

<table>
<thead>
<tr>
<th>Tumor markers in 301 carcinoid patients.</th>
<th>Percentage increased Median level Refs range</th>
</tr>
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<tbody>
<tr>
<td>Midgut</td>
<td></td>
</tr>
<tr>
<td>U-5 HIAA</td>
<td>75</td>
</tr>
<tr>
<td>p-chromogranin A</td>
<td>87</td>
</tr>
<tr>
<td>p-neuropeptide K</td>
<td>46</td>
</tr>
<tr>
<td>Foregut</td>
<td>31</td>
</tr>
<tr>
<td>U-5 HIAA</td>
<td>85 μmol/24 hours</td>
</tr>
<tr>
<td>p-chromogranin A</td>
<td>79</td>
</tr>
<tr>
<td>p-neuropeptide K</td>
<td>9</td>
</tr>
<tr>
<td>Hindgut</td>
<td>0</td>
</tr>
<tr>
<td>U-5 HIAA</td>
<td>33 μmol/24 hours</td>
</tr>
<tr>
<td>p-chromogranin A</td>
<td>100</td>
</tr>
<tr>
<td>p-neuropeptide K</td>
<td>7</td>
</tr>
</tbody>
</table>

**Treatment**

The basis for therapy in neuroendocrine gastrointestinal tumors are not only curative intent but merely amelioration of clinical symptoms, abrogation of tumor growth and maintaining and improving quality of life. Different means of treatment have to take into consideration the stage of the disease and tumor biology. This is indicated in Figure 2 for patients with midgut carcinoids.
Diagnostic work up

Carcinoid suspected

Biochemical diagnosis [CgA, 5-HIAA]

Flush provocation
Pentagastrin; NPK; Subst-P

Localization:
Somatostatin receptor scintigraphy (SRS)

Histopathology:
CgA, Synaptophysin, 5-HT

US: liver + biopsy
CT-scan, MRI

Follow-up

Therapy

Figure 1. Diagnostic work up.

Therapeutic alternatives in carcinoid tumors.

Surgery

In the treatment of neuroendocrine gut and pancreatic tumors surgery is always considered. Resection of local disease or resection of regional nodular metastatic disease can result in cure for some patients [9]. Even if radical surgery can not be performed debulking procedures and bypassing should always be considered and can be performed as needed during medical treatment. Recently the surgical approach has been more aggressive including wide resections of mesenteric metastases, together with enucleation of liver metastases or even hemo-hepatectomy. Small series of liver transplantations for carcinoids are available but the long-term results are not convincing [10].

Liver dearterilisation

In order to reduce the bulk of liver metastases embolisation with Spongostan or Gel foam of the hepatic artery is rather effective with response rates of 50%-70% and a median duration of response of 9–12 months [11]. The procedure can be repeated and also include cytotoxic agents (chemoembolisation) [12].

Irradiation

External irradiation is only effective to treat brain and bone metastases. Therapy with radioactive I\textsuperscript{125}-MIBG has been applied for carcinoids with varying results (30%-50%) biochemical responses [13]. Recently Ind\textsuperscript{111}-DTPA-octreotide has been applied in malignant neuroendocrine tumors. Preliminary data indicate response rates of 30%-60% depending on patient inclusion. Tumors with higher grade (grade 3 or 4) of uptake of radioactive octreotide show higher response rates [14] (see the present paper by Krenning et al. in this supplement).

Medical treatment of neuroendocrine tumors

Since the majority of patients present metastatic disease at time of diagnosis surgical treatment, although being the 'gold-standard' is not curative. The causal medical treatment includes mainly chemotherapy, somatostatin analogues and α-interferons.

Chemotherapy

Chemotherapy of carcinoids and pancreatic endocrine tumor has usually been reported in studies involving a limited number of patients with variable criteria for assessing antitumor responses. Furthermore, many studies have not taken into consideration the different biological behaviour of midgut carcinoids and pancreatic endocrine tumors, both types sometimes being evaluated together in the same study.

Single agent chemotherapy for carcinoid tumors including streptozotocin, doxorubicin, fluorouracil, dacarbacin, actinomycin and cisplatinum has only generated short-lasting responses in 0%-26% of the patients. Combination chemotherapy trials have not been more successful than single agents and includes combinations of streptozotocin plus 5-fluorouracil (5-FU), Sendoxan or doxorubicin and etoposide combined with cisplatinum. The response rates are still low and short-lasting in the range of 10%-30% [15-17]. In contrast to the experience of chemotherapy for carcinoids is the occasional remarkable success for endocrine pancreatic tumors. Streptozotocin based combination has been basis for chemotherapy in malignant endocrine pancreatic tumors. Combinations with 5-FU and doxorubicin have generated partial remissions in 40%-60% of the patients, giving remissions for almost two years and a median survival of about two years in larger studies. In the last years trials with combinations of etoposide and Cisplatinum in patients with poorly differentiated neuroendocrine tumors have been quite
successful. The response rate was 67% for anaplastic tumors with a median duration of 18 months, whereas the response rate for well differentiated carcinoid tumors or islet cell carcinomas was only 7% [16, 18, 19].

Liver-targeted chemotherapy has been attempted over the years and the Mayo Clinic reported on a study where hepatic artery occlusion was followed by treatment with doxorubicin, dacarbacin followed by streptozotocin and 5-FU in an alternate way which was repeated every four to five weeks. In 21 patients with malignant carcinoid tumors 19% complete biochemical responses was recorded and 57% partial remissions. Similarly in 11 patients with islet cell carcinomas, 64% complete biochemical response and 18% partial remissions were observed. The duration of the biochemical response was estimated at a median of 24 months. The adverse reactions were considerable and these preliminary data need confirmation.

**Somatostatin analogues** (for details, see the paper by Schonbrunn and Eriksson in this supplement)

The observation that somatostatin inhibits the release of various peptide hormones has stimulated interest in its use as an antiproliferative agent. Somatostatin inhibits the release of several intestinal peptides and indirectly through actions on growth hormones it also modulates growth factors like IGF-1 and -2 [20].

Somatostatin and its analogues can exert antiproliferative effects on endocrine tumors by at least three mechanisms: a) inhibition of release of peptides from the pituitary, intestine, pancreas or b) direct antagonism of growth factor effects on tumor cells. c) recently we have been able to show that high-dose somatostatin analogues might induce apoptosis [21]. Somatostatin and its analogues exert their effects through somatostatin receptors and at present five subtypes are identified with 50%-60% homology. All receptors belong to the seven transmembrane receptor family signalling through G-proteins. Somatostatin 14 binds to all five subtypes whereas the most common somatostatin analogue octreotide Sandostatin binds to somatostatin receptor 2 and 5. Somatostatin receptor 2 seems to mediate antiproliferative effects in cell lines.

Because of the short half-life of natural somatostatin (three minutes) it is not convenient to use clinically and therefore, during the last decade somatostatin analogues have been developed. The most common and widely used is octreotide (Sandostatin) but other somatostatin analogues including somatuline (BIM 230146) and octastatin (RC-160) are also available. All these analogues are octapeptides and the biological action and binding through somatostatin receptor reside in only four amino-acid residues within the ringstructure of somatostatin. The half-life for these analogues is about two to three hours and can be administered subcutaneously. Recently long-acting formulations have been developed with formulation by microcapsules, thus giving intervals between the injection of two to four weeks. Somatostatin receptor scintigraphy is an important invention during the last years and T$_{99m}$indium labelled DTPA octreotide is an important tool in both diagnosing neuroendocrine tumors and also in guiding the use of medical treatment. Our group has recently shown that lack of somatostatin receptor type 2 is accompanied by lack of tumor response for octreotide [22].

Octreotide is registered in most countries for treatment of patients with the carcinoid syndrome and also VIP-producing tumors and glucagonomas. The drug is mainly giving biochemical responses and related clinical improvements. In carcinoid patients the biochemical response rates varies between 30%-75% depending on the dose. The optimal dose for controlling clinical symptoms is about 100–150 µg two to three times per day. Experimentally high dose treatment with doses of 3000–18,000 µg/day has been applied without an increase in biochemical response rates but sometimes higher figures of tumor reduction (10%-15%). Similar doses have been applied for pancreatic endocrine tumors. In emergency situations intravenous infusion of somatostatin analogue can be used at doses of 50–100 µg/hour [23-25].

The side effects of octreotide treatment is generally mild. It includes fat malabsorption, development of gallbladder dysfunction and D-vitamin malabsorption. Pain at injection site is one of the major reasons for the patient to stop the treatment and another negative factor is that the drug has to be given several times per day. Tachyfylaxis to the drug is also common.

**Interferon**

Interferon is one of the defence mechanisms of the body. Its production is a cellular response to substances such as microbes, tumors and antigens. Alpha-interferon has been mainly applied in viral and tumor diseases. Very few solid tumors have demonstrated sensitivity to α-interferons but in patients with renal cell cancer, malignant melanoma and colorectal cancer there have been reports of some antitumor effects. Neuroendocrine gut and pancreatic tumors are an exception to other solid tumors in which α-interferons have demonstrated sensitivity to α-interferons but in patients with renal cell cancer, malignant melanoma and colorectal cancer there have been reports of some antitumor effects. Neuroendocrine gut and pancreatic tumors are an exception to other solid tumors in which α-interferons have demonstrated antitumor effects in around 50% of the patients. More than 300 patients have been reported in the literature today being treated with various types of α-interferons, both leukocyte alpha-interferon and recombinant interferon-α2a and -2b with similar results. Biochemical responses is encountered in a median of 40%-50%, symptomatic improvement in 40%-70% of the patients and significant tumor shrinkage in a median of 10%-15% of the patients. The dose of α-interferon should be median sized which means 3–5 MU/m$^2$ three to five times per week. The treatment should continue for long-term and at our unit we have treated patients continuously for more than 10 years. Significant impact on survival has also been noticed [26-29].

Recently α-interferon has been combined with soma-
in analogues with significant potentiation of the effects. In a group of patients with resistance to octreotide analogues the addition of α-interferons (5 MU three times per week) generated biochemical responses in 77% of the patients, 18% complete responses. Again no significant tumor reduction was observed. The reasons for discrepancy in biochemical responses might be that interferon induces fibrosis within the tumor which will not decrease tumor size on CT-scan or ultrasound but can easily be recognized on biopsies as well as positron emission tomography.

Adverse reactions of α-interferon treatment include mainly flu-like symptoms initially for three to five days which are easily managed by paracetamol. More adverse reactions are the chronic fatigue syndrome and 50% of the patients which sometimes necessitate dose reductions. Other adverse reactions might be neopterinemia, which is easily measured in the urine of patients with carcinoid tumors: An analysis of 103 patients with regard to pathological findings in 84 patients. J Intern Med 1990; 228: 103-12.


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