Review

Neuroendocrine gastrointestinal tumours

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Summary

Neuroendocrine gut and pancreatic tumours have provided a diagnostic and therapeutic challenge over the years. These rather slowly growing neoplasms have been assigned a good prognosis but when liver metastases are present the prognosis is not better than that of most other malignant tumours. Despite the development of improved diagnostic procedures many patients are still referred at a stage of the disease too late for surgical cure, at which time medical treatment is warranted. The diagnosis is based on histopathological diagnosis including silver stainings (Grimelius, Masson) and immunohistochemistry for chromogranin A and synaptophysin. Analysis of chromogranin A in the plasma is an important adjunct in the screening for various types of neuroendocrine gut and pancreatic tumours. About 80%-100% of patients with verified neuroendocrine gastrointestinal tumours have elevated circulating levels of this glycoprotein. Depending on clinical symptoms the chromogranin A analysis is supplemented by other peptide hormone analyses as well as urinary 5-HIAA for patients with midgut carcinoid tumours. In the past the localization procedures were based on CT, MRI and ultrasound investigations but in recent years somatostatin receptor scintigraphy (octreoscan*) and endoscopic ultrasonography have significantly improved the diagnostic potential. Almost 80% of neuroendocrine gastrointestinal tumours present somatostatin receptor subtype 2 binding 111In-labelled octreotide which can be used for staging of the disease, and which also indicates whether or not somatostatin analogues can be used in the treatment of these tumours. Surgery is still a cornerstone in the treatment of neuroendocrine gastrointestinal tumours, even if the patients are beyond cure. Debulking procedures and bypassing operations are important for improving clinical condition and facilitating impending medical treatment, and during the past decade a more aggressive surgical approach has emerged. The medical treatment is based on chemotherapy, and the use of somatostatin analogues and alpha-interferons. Chemotherapy, in particular the combination of streptozotocin with 5-FU or doxorubicin, is still first-line treatment for most endocrine pancreatic tumours, while somatostatin analogues and alpha-interferons are considered first-line for classical midgut carcinoids. Chemotherapy and biotherapy can be combined in many patients, and changes from one medical treatment to another during the course of the disease is mandatory for control of the disease. It is important to realise that most patients with malignant tumours are not cured by medical treatment but that the disease can be controlled for extended periods of time. In the future it will be possible to individualize treatments on the basis of new information about such features of tumour biology as proliferation capacity, expression of adhesion molecules, and growth factors and their receptors.

Key words: α-IFN, carcinoids, chromogranin A, endocrine pancreatic tumours, neuroendocrine gastrointestinal tumours, octreoscan, somatostatin analogue

Introduction

Neuroendocrine gastrointestinal tumours derive from the neuroendocrine cell system and have widely divergent clinical presentations. These tumours are rare – the most common type, the carcinoids, occurs in 2.8 to 21 per 1,000,000. The incidence of carcinoid syndrome is about 0.5 per 100,000 and for endocrine pancreatic tumours 0.4 per 100,000 [1, 2]. The neuroendocrine gastrointestinal tumours are divided into two main groups, carcinoids and endocrine pancreatic tumours. The carcinoids are then divided into foregut, midgut and hindgut carcinoids [3], while the endocrine pancreatic tumours have been designated according to their main hormone production and related clinical syndrome e.g., insulinomas, gastrinomas, VIP-omas, glucagonomas, somatostatinomas and non-functioning islet cell tumours. Foregut carcinoid tumours include those with primaries located in the lung, stomach and proximal duodenum, whereas midgut carcinoid tumours arise from the rest of the small intestine and proximal colon. Hindgut carcinoid tumours comprise those originating in the distal part of the colon and rectum [4]. This classification, which is based on the anatomical localisation of the tumour, has been questioned of late, and to eliminate the present confusion the term carcinoid might in future be used to designate traditional midgut neuroendocrine tumours with the carcinoid syndrome. Other tumours should be assigned the term ‘neuroendocrine tumours’ followed by their primary location, e.g., neuroendocrine lung, gastric, duodenal, pancreatic, colonic and rectal tumours. The
dominant hormone production may sometimes be included, e.g., gastrin-producing neuroendocrine duodenal tumour, etc. Such a classification would certainly be helpful in communicating information about these tumours and also in evaluating therapy studies.

Multiple endocrine neoplasia type 1 (MEN I) is a familial disorder, inherited as an autosomal dominant trait with variable penetrance patterns [5]. In MEN 1 the pituitary, parathyroids and endocrine pancreas are most commonly affected, but the adrenal cortex and the thyroid can also be involved. A specific genetic deletion [6, 7] has been described for MEN 1 (see below) and around 80% of affected MEN 1 patients develop endocrine pancreatic tumours [8]. Furthermore, about 30% of all gastrin-producing neuroendocrine gastrointestinal tumours are related to the MEN 1 syndrome [9]. Some of these patients also develop lung, duodenal or gastric carcinoids [8, 10].

Neuroendocrine gut and pancreatic tumours present various clinical symptoms related to hormone production. The most common clinical syndrome is the carcinoid syndrome which may be present in patients with midgut carcinoid tumours with liver metastases as well as in some patients with foregut carcinoid tumours [11-13]. The syndrome consists of flushes, diarrhoea, carcinoid heart disease with right heart failure, bronchial constriction and elevated levels in the urine of the serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA). The tumours also release tachykinins, bradykinin and prostaglandins. In some patients the syndrome is severe enough to be potentially life threatening, with extensive flushing combined with hypotension or very frequent diarrhoea - the so-called carcinoid crisis. Forty percent of all carcinoids are in the midgut.

Pancreatic endocrine tumours are classified as functioning if they are associated with a clinical syndrome related to hormone production, and are considered non-functioning if they are not associated with a clinical symptom of hormone release. The latter category constitutes around 30% of all endocrine pancreatic tumours and includes tumour secreting pancreatic polypeptide (PP), chromogranin A, peptide YY (PYY) and neurotensin [2]. The two most clinical syndromes most commonly related to endocrine pancreatic tumours are the Zollinger Ellison syndrome, caused by gastrin over-production [9, 14], and the hypoglycemic syndrome, which is related to high insulin/proinsulin release [15-17]. The Zollinger Ellison syndrome or gastrinoma syndrome can also be confined to gastrin production by duodenal carcinoids (around 40%) and more than 70% of gastrin-producing tumours are malignant, with early lymph node involvement [9, 14]. Clinical symptoms related to gastrin production are gastritis, diarrhoea and malabsorption, but severe gastric ulcer disease is rare today due to the extensive use of H2-receptor blockers and proton pump inhibitors. Most neuroendocrine tumours with hypoglycemic syndrome are related to the increased production and release of insulin and proinsulin [15-17]. They may also be related to sarcomas producing IGF-1/IGF-2. Eighty per cent of these tumours are benign solitary tumours in the pancreas and the patient can be cured by surgery. Twenty percent of the tumours are malignant, with distant metastasis, and produce peptide hormones other than insulin/proinsulin, such as gastrin, ACTH and glucagon [2]. Typical symptoms related to insulin over-production are signs of neuroglucopenia and increased catecholamine release. Other functioning endocrine pancreatic tumours are VIP-producing tumours causing the so-called Verner Morrison syndrome or WDHA syndrome, accompanied by extensive diarrhoea, hypokalemia and acalorhydria [18-20]. In such patients the stool volume might reach more than 10 litres per day and they often require intensive care. The tumours are confined to the pancreas but sometimes also to the lung or sympathetic ganglia [19]. Another rare clinical syndrome is the glucagonoma syndrome with a typical necrolytic migratory erythema, diabetic glucose tolerance, anaemia, weight loss and tromboembolism, all signs related to glucagon production and the effects of glucagon [21, 22]. Somatostatin-producing tumours can be both functional and non-functional [23]. Syndromes with gall bladder dysfunction, gall stones and diabetic glucose tolerance, malabsorption and diarrhoea are sometimes related to increased levels of circulating somatostatin. However, an increased level of plasma somatostatin is quite often found in patients with so-called non-functioning islet cell tumours [24].

Foregut carcinoids comprise 15% of all carcinoid tumours and include thymic and lung carcinoids, but they will not be discussed in this review. Most gastrointestinal foregut carcinoids are confined to the gastric and duodenal mucosa. Duodenal carcinoids sometimes secrete gastrin and somatostatin and produce related symptoms. There are three separate groups of gastric carcinoids. One group is related to chronic atrophic gastritis with acalorhydria and increased gastrin production from antral G-cells. Gastrin stimulates the proliferation of ECL cells, with the formation of multiple polyps in the corpus/fundic region of the stomach (ECL-omas). These tumours are essentially benign and may secrete histamine and chromogranin A. A second type of gastric carcinoid is the so-called mixed type which includes neuroendocrine carcinomas; these always have a potential for malignancy and are not related to chronic atrophic gastritis. The third type is related to MEN I and also exhibits a malignant phenotype [25, 26].

Hindgut carcinoids constitute 20% of the carcinoids and belong to the group of non-functioning neuroendocrine tumours. Despite their production of hormones such as chromogranin A, PYY, HCG-α/β subunits, they produce no related clinical symptoms [4, 27]. They present clinical symptoms such as bleeding, intestinal obstruction or an abdominal mass which cannot be distinguished from those of colorectal cancer. A special type of midgut carcinoid is the appendiceal car-
cinoid which is quite often found incidentally at appendicectomy and tumours smaller than 2 cm are always benign. However, appendiceal carcinoids confined to the base of the appendix should be regarded as regular midgut carcinoids with metastatic potential which warrant extended surgery [28].

Tumour biology and histopathology

Neuroendocrine tumours have been called APUDomas. The APUD (amine precursor uptake and decarboxylation) concept was originally introduced in 1974 by Pearse who found that cells of neural crest origin migrate during their embryonal development into other tissues including the intestinal tract, pancreas and several endocrine glands [29]. These specialized cells accumulate amine precursors (DOPA or 5-hydroxytryptophan) and decarboxylate them to produce biogenic amines (cathecolamines or serotonin); these cells also produce peptides. The APUD concept was later abandoned by most researchers but it continues to provide a convenient framework for explaining the multipotential capacity of these cells to produce various hormones and amines. Classical midgut carcinoids develop from so-called enterochromaffin cells (EC cells) in the mucosa of the small intestine, whereas hindgut and foregut carcinoids can develop from either pluripotent stem cells or already differentiated neuroendocrine cells in the various regions of the gastrointestinal tract. In the pancreas the D1 cell in the pancreatic islet has been considered as a stem cell for the development of various kinds of neuroendocrine tumours [30]. Another theory is that pluripotent stem cells originating in the pancreatic duct may develop into either exocrine or endocrine pancreatic cells [31]. This theory is supported by observations from our lab where gastrin-producing tumours, exocrine pancreatic and pancreatic duct cells have been found to be positive for the adhesion molecule CD44, while other islet cell tumours and the pancreatic islets are completely negative [32]. Gastrin-producing cells are not found in adult pancreas, so we speculate that endocrine pancreatic tumours which present a malignant phenotype develop from such stem cells in the pancreatic ducts, whereas the benign insulinomas might develop from differentiated islet cells. Benign insulinomas are negative for CD44. Expression of larger molecular forms of CD44 which are stained by the antibody H-CAM are related to malignant potential in other tumour types as well.

In multiple endocrine neoplasia type 1 (MEN 1) we were able to locate the specific genetic deletion to chromosome 11 q13 (PYGM) [6, 7]. Recently we cloned a candidate gene, PLC-β3, from this region which we believe might be a new tumour-suppressor gene. It is down-regulated in MEN 1 endocrine pancreatic tumours, parathyroids and pituitary tumours but also in some sporadic cases of lung and gastric carcinoids and sporadic endocrine pancreatic tumours [33]. PLC-β3 is one of the key enzymes in the signal transduction pathway from G-protein-coupled receptors and most peptide hormones and amines signal through such receptors. Furthermore, neuroendocrine gut and pancreatic tumours express a number of different traditional growth factors such as IGF-1, PDGF-α, b-FGF, TGF-α and the TGF-β family. PDGF-α and β receptors are expressed on both tumour cells and tumour matrix, indicating paracrine and autocrine loops, whereas the b-FGF and TGF-β families are mostly expressed in the matrix component of the tumour [34]. Expression of the PDGF-α receptor is a poor-prognosis factor in epithelial ovarian cancer [35] and the possibility that the same is true for neuroendocrine gut and pancreatic tumours is being studied. DNA analyses of tumours have been of limited value since most of them show diploid characteristics [36]. However, the nuclear antigens Ki-67 and PCNA have been useful for delineating the proliferative capacity of various neuroendocrine tumours [34, 37]. Most classical midgut carcinoids show a low proliferation index, whereas endocrine pancreatic tumours demonstrate more heterogeneous patterns. High Ki-67 staining is related to a significantly shorter survival in patients with midgut carcinoid tumours [34].

The histopathological diagnosis of neuroendocrine gut and pancreatic tumours is based on silver stainings; the argyrophil staining by Grimelius which is a general marker for neuroendocrine differentiation and the argentaffin staining by Masson to demonstrate content of serotonin [4]. During the last decade immunohistochemistry with antibodies against chromogranin A and synaptophysin have been important to delineate the neuroendocrine features of these tumours. All well differentiated neuroendocrine gastrointestinal tumours show positive staining for chromogranin A antibodies except some insulin-producing tumours which might be stained by chromogranin B antibodies. Synaptophysin shows similar sensitivity but this antibody has to be used on frozen sections rather than formalin-fixed material, which limits its clinical use. Some neuroendocrine cancers stain only weakly-positive with both silver stainings and chromogranin A antibodies and therefore electronmicroscopy might be of value to show the content of secretory granules. Neuron-specific enolase (NSE) has been considered a specific marker for neuroendocrine tumours. Unfortunately, it also stains certain non-neuroendocrine tumours and should therefore be combined with some of the other methods described above. Histopathological diagnosis is the basis for therapeutic considerations.

Biochemical diagnosis

With the introduction of radioimmunoassays for various peptide hormones in the mid-1960s, clinical awareness of and ability to diagnose neuroendocrine gastrointestinal tumours increased. During the succeeding decades more or less specific radioimmunoassays were developed for various hormones, and every
laboratory made panels of different radioimmunoassays. The past decade has seen the emergence of more stringent indications for the use of hormone analysis, partly due to cost constraints. Today the most important biochemical marker for screening of neuroendocrine tumours is analysis of chromogranin A. Between 80% and 100% of patients with verified neuroendocrine tumours have shown increased levels of chromogranin A (Tables 1 and 2, Figure 1) [38, 39]. Chromogranin A belongs to a family of glycoproteins which includes chromogranin B and C. Pancreastatin is a splice product of chromogranin A. Chromogranin B and C. Pancreastatin instead of chromogranin A but plasma pancreastatin is a less sensitive marker for neuroendocrine tumours (Figure 1) [39]. This may reflect the inability of certain tumour cells to produce pancreastatin because of a lack of essential cleavage enzymes due to low differentiation in the tumour.

Urinary 5-HIAA, the breakdown product of serotonin, is still an important marker for midgut carcinoid tumours (Tables 1 and 2) and a combination of urinary 5-HIAA and plasma chromogranin A can be used to diagnose all clinically significant midgut carcinoid tumours [40]. Takykinins such as neuropeptide K and substance P are also increased in midgut carcinoids but to a lesser extent and might be an adjunct in the diagnosis and follow-up of patients with flushing [41]. Pancreatic polypeptide has been considered an important marker for endocrine pancreatic tumours and is increased in around 60% of patients with these tumours [2]. Unfortunately, it is very unspecific and its elevation may be caused by diarrhea or diabetes mellitus. HCG-α and β subunits are increased in 20%-30% of the patients and might be a predictor of bad prognosis [2, 40].

In some patients the biochemical diagnosis may not be clear and therefore various stimulatory tests have been developed. Secretin stimulation of gastrin release in patients with suspected Zollinger Ellison syndrome, positive in up to 80% of the patients, is significant [41]. A meal stimulatory test for pancreatic polypeptide secretion in patients with endocrine pancreatic tumours has been helpful in diagnosing endocrine pancreatic tumours at an early stage, particularly in members of families with MEN 1 tumours [42]. Also useful is pentagastrin stimulation to provoke a flush reaction in midgut carcinoid patients with a low frequency of spontaneous flushing, with measurement of neuropeptide K [43]. A small percentage of patients with hypoglycemic symptoms need 48–72 hours of fasting with measurements of b-glucose insulin and pro-insulin for disclosure of the diagnoses [2].

**Localization procedures (Table 1)**

Basically, computerized tomography, magnetic resonance imaging and ultrasound investigations are the cornerstones for the localization of neuroendocrine gut
and pancreatic tumours [44, 45]. Tumours located in the stomach and duodenum can be visualized and localized by gastroscopy, and hindgut and some midgut carcinoids can be found at colonoscopy. About 1/3 of patients with classical midgut carcinoids suffer from intestinal obstruction and a barium enema can be instructive. Small tumours in the pancreas are very difficult to localize; angiography and portal venous sampling with analysis of hormones from various parts of the pancreatic circulation were formerly used for this [46] but these investigations are expensive and cumbersome and have now been replaced by new techniques. Somatostatin receptor scintigraphy (Octreoscan®) is useful for localizing most neuroendocrine gastrointestinal tumours [47, 48]. About 80% of the tumours present somatostatin receptors, particularly type 2 receptors (sst₂) which bind [¹¹⁳I-In-DTPA-D-Phe¹] Octreotide. The detection limit is about 0.5 cm but besides giving the localization it also provides information about the somatostatin receptor status. It is a whole body investigation and thus provides a better tumour staging than conventional methods. Endoscopic ultrasonography has recently come into clinical use and its potential has not yet been fully realized but it can demonstrate and localize small (2–3 mm) endocrine pancreatic tumours as well as duodenal carcinoids [49]. Positron emission tomography (PET) using ¹¹C-labelled 5-HTP and L-dopa has been developed at our institution and has proven to be quite effective in localizing carcinoids and endocrine pancreatic tumours as small as 0.5 mm [50]. It also provides information about the metabolism of the tumours, since 5-HTP is a precursor of serotonin synthesis. The investigation is rather expensive but in the future it will be possible to label most substances with short-lived isotopes for obtaining information about the tumour biology directly in the patient, replacing other investigations.

**Treatment**

Consideration of the treatment of neuroendocrine gastrointestinal tumours always includes the possibility of surgery. Resection of local disease or of regional, nodu-
lar metastatic disease can cure some patients, but even if radical surgery can not be performed debulking procedures and bypassing should always be considered and can be performed at any time during the course of treatment [51-54]. In recent years a more ‘active’ attitude among surgeons has emerged and in general more wide resections and debulking procedures are performed today than 10 years ago [55]. Liver transplantation in suitable cases has also been considered, but this procedure needs further evaluation before it can be incorporated in the general management of neuroendocrine tumours [56]. The greatest concern among surgeons is about gastrin-producing tumours, particularly in combination with the MEN 1 syndrome with multiple primary tumours [57, 58]. The reason for a conservative approach is that the clinical symptoms can today be easily managed by proton pump inhibitors and H₂-receptor blockers as well as biotherapy. However, gastrin-producing tumours always have a malignant potential and resections are indicated when feasible. A prerequisite for surgery is always an optimal localization which today includes intraoperative ultrasound during operation.

In general external radiation therapy has not been successful in the treatment of metastatic neuroendocrine tumours, except for treatment of symptomatic bone, skin and brain metastases [59]. Carcinoid tumours have been treated with local irradiation such as ¹²⁵I-MIBG with some success particularly in patients with high uptake rates [61, 62]. Most recently high-dose treatment with [¹¹¹In-DTPA-D-Phe⁴] octreotide has been attempted but it is still too early to know what its ultimate role in treatment will be (to be published).

Hepatic artery ligation, surgical or by embolisation (Spongostan®, Ivalon®) has been reported to reduce hepatic tumour bulk [63, 64]. In general, biochemical responses occur in about 50% of the patients with or without regression of hepatic metastases. The duration of response is generally short, usually about 3–9 months. So-called chemoembolisation has been performed in some studies whereby embolisation or hepatic artery ligation is combined with chemotherapy with dacarbacin, doxorubicin, 5-fluorouracil (5-FU) and streptozotocin. Such procedures have led to long-lasting responses in some patients but their precise role has still to be defined [65, 66].

**Medical treatment (Table 3)**

The medical treatment of neuroendocrine gut and pancreatic tumours includes chemotherapy, somatostatin analogues and alpha-interferons. Because of the rarity of these tumours studies have been frequently reported in a very tenuous fashion. Furthermore, many of the studies do not take into account the difference in biological behaviour between classical midgut carcinoids and endocrine pancreatic tumours and evaluate the two types together. Pure symptomatic therapy such as H₂-receptor blockers, proton with pump inhibitors, loperamid, etc., will not be discussed in this review. Many patients present metastatic disease at the time of diagnosis, when surgery can no longer cure them, and medical treatment is then warranted. Endocrine gut and pancreatic tumours have been assigned good prognoses and many physicians have therefore been reluctant to administer medical treatment at early stages of the disease. However, a critical look at the 5-year survival rates in patients with malignant neuroendocrine tumours shows 5-year survival rates of less than 20% when liver metastases are present. The median survival for patients with malignant carcinoid tumours with the carcinoid syndrome was earlier reported to be less than 2 years from diagnosis of a carcinoid syndrome [28, 66, 68].

**Chemotherapy**

In patients with endocrine pancreatic tumours, which comprise a very heterogeneous group, single-agent chemotherapy including streptozotocin, doxorubicin, 5-fluorouracil, dacarbacin and cisplatinum has generated response rates between 7% and 25%. However, when streptozotocin has been combined with 5-fluorouracil the response rate has increased to 60%, and with the combination of streptozotocin plus doxorubicin even higher, with 69% objective responses [69-75]. When the same combination of chemotherapeutic drugs was applied in patients with classical carcinoid tumours the response rates were only 10%-30% and were very brief, generally less than 3 months [76-90]. This should be compared with the protracted responses in endocrine pancreatic tumour patients of more than 2 years. Anaplastic neuroendocrine tumours might benefit from treatment with the combination of cisplatinum and etoposide [91]. No objective response was noted in patients with classical carcinoid tumours but 67% of 18 patients with anaplastic neuroendocrine tumours showed objective responses. This combination seems promising for more aggressive neuroendocrine tumours but needs further evaluation. The side effects are considerable. Other chemotherapeutic drugs such

| Table 3. Medical treatment in patients with neuroendocrine GEP-tumours. |
|---------------------------------|-----------------|-----------------|
| First line                      | Second line     |
| Endocrine Pancreatic Tumors     | STZ + 5-FU      | SOM ± αIFN      |
| (EPT)                           | STZ + DOX       |                 |
| Anaplastic EPT                  | STZ + DOX       | Cispl + Etop    |
|                                | alt             | STZ + 5-FU      |
|                                | Cispl + Etop    | STZ + αIFN      |
| Midgut carcinoids               | αIFN ± SOM      | Cispl + Etop    |
| Hindgut carcinoids              | αIFN ± SOM      | Cispl + Etop    |

STZ = streptozocin; DOX = doxorubicin; 5-FU = fluorouracil; Cispl = cisplatinum; Etop = etoposide; α-IFN = alpha-interferon; SOM = somatostatin analogue; NB = somatostatin analogues can always be combined with chemotherapy and/or α-IFN.
as Taxol, Fotemustine and Maytansin have been tested in individual patients, with scattered responses. Chemotherapy is still the first-line treatment in malignant endocrine pancreatic tumours and foregut carcinoids and the choice between the combinations of streptozotocin, 5-FU and doxorubicin, or cisplatinum and etoposide might be based on tumour biology factors such as high proliferation index (Ki-67). In classical midgut carcinoid tumours with a low proliferation index chemotherapy should be avoided and biological treatments such as with somatostatin analogues and alpha-interferons should be considered instead.

**Somatostatin analogues**

The observation that somatostatin inhibits the release of various peptide hormones has stimulated interest in its use as an antiproliferative agent [91]. Natural somatostatin 14 has a short half-life of about 2 minutes and is not suitable for clinical use. Analogues of somatostatin with longer half-lives (2–3 hours at s.c. administration) were developed in the past decade. They are all octapeptides, and keep the receptor binding site intact. The clinically available analogues (octreotide, lanreotide, RC-160) all bind to receptor subtype 2 (sst2) and 5 (sst5). At present five different subtypes of somatostatin receptors have been cloned and receptor (sst2) is believed to mediate the antiproliferative effect as well as inhibition of hormone synthesis and release [92]. Several signal transduction pathways are antagonised by somatostatin and its analogues, including second messengers such as cyclic AMP, diacylglycerol (DAG), calcium and potassium channel actions and tyrosin phosphatase activation. The receptors are so-called seven transmembrane receptors coupled to G-proteins [92–95].

Octreotide (Sandostatin®) has been clinically the most commonly applied somatostatin analogue, yielding biochemical response rates in the range of 30%–70% but objective tumour shrinkage in less than 10% of the patients [96–101]. The other analogues, lanreotide and RC-160, yield similar response rates (to be published). High-dose somatostatin analogue treatment (>3000 µg/day) might induce apoptosis in neuroendocrine tumours, a possibility which should be explored in forthcoming clinical trials (to be published). Somatostatin analogue treatment produces subjective improvement in more than 70% of patients at regular doses of 150–300 µg/day. It is well tolerated with only a few side effects such as gall bladder dysfunction, gall stones and, in isolated cases, also hypocalcemia. Caution should be observed in patients with hypoglycemic syndromes since octreotide might block counter regulatory mechanisms such as growth hormone and glucagon more efficiently than insulin secretion. However, malignant insulin-producing tumours sometimes show quite significant biochemical response to somatostatin analogues.

In summary, somatostatin analogue treatment has been a real breakthrough in the treatment of neuroendocrine gut and pancreatic tumours. Clinical symptoms can easily be controlled over long periods of time, even though takyfylaxis may develop with time. The drug is generally well tolerated. High-dose treatment might generate more tumour responses in the future.

**Interferons**

Interferon alpha was introduced by our group in treatment of carcinoid tumours in 1982 because of its ability to stimulate natural killer cell function, and to control hormone secretion, clinical symptoms and tumour growth [102]. Since then more than 350 patients with neuroendocrine tumours have been treated with interferon alpha in our institution and as many have been reported in the literature [102–114]. Natural human leukocyte interferon contains more than 15 subtypes of alpha-interferons, whereas the recombinant interferons alpha 2b, (Intron-A) 2a, (Roferon) and 2c contain one subtype of interferon. The applied doses of alpha-interferon have been 3–9 MU 3–7 times per week subcutaneously. We are trying to titrate the dose to the individual patient, to reduce the leukocyte count down to 3.0 × 10^9/l. By using such titrations the response rates in endocrine pancreatic tumour patients have been 51% biochemical responses and 12% significant tumour reduction. The median duration of response was 20 months. In carcinoid tumours, predominantly classical midgut carcinoids the biochemical response was 42% with a median duration of 32 months. Another 39% of the patients showed stabilization of their diseases with no further tumour growth. Only 15% of the patients demonstrated significant reduction of tumour size, whereas 70% experienced a subjective improvement with less flushing and/or diarrhoea. Survival data in our patients with malignant carcinoid tumours showed a median survival from start of treatment of >80 months which is 10 times longer than that of a historical group of patients treated with chemotherapy (streptozotocin plus 5-FU) reaching a median survival of only 8 months [114]. Similar response rates have been reported by other groups in carcinoid tumour patients [112, 115]. The side effects of alpha-interferon include chronic fatigue syndrome, flue-like symptoms for the first 3–5 days and slight anaemia and increased liver enzymes in 15%–20% of the patients. Most of the side effects are dose-dependent and were reduced by dose adjustments. Recently several centres have started combination trials in carcinoid patients whereby alpha-interferon is combined with somatostatin analogues. In a recent study from our institution 77% of patients resistant to octreotide alone showed biochemical remissions when alpha-interferon at a dose of 9 MU per week was added [116]. However, we saw no increase in the number of tumour responses with this combination.

The mechanism of action of interferon is related to cell cycle blocking in G0 and G1 phase, induction of 2'-5'-A-synthetase and thereby reduction of mRNA for
hormones and growth factors [117, 118]. Furthermore, induction of class I antigens on the cell surface together with general stimulation of the immune system might account for the antitumour effect of alpha-interferon. Alpha-IFN also induces fibrotic reactions within the tumour [119].

To summarize, alpha-interferons have demonstrated antitumour effects in neuroendocrine gut and pancreatic tumours. It has a stronger antiproliferative effect than somatostatin analogues at current doses but by combining alpha-interferon and somatostatin analogues the response rates might be further improved. Alpha-interferon is better tolerated by the patients when combined with somatostatin analogues.

**Future therapeutic perspectives**

Long-acting formulations of somatostatin analogues is about to be introduced into clinical trials. These somatostatin analogues might be injected only once every four week intramuscularly instead of 3 times per day subcutaneously. That will of course improve the quality of life in many patients. High-dose treatment with somatostatin analogues, probably in combination with alpha-interferon, should generate more antitumour responses with sustained effects. At our institution tumour biology-based treatment has now been introduced whereby the patients receive a tailor-made treatment based on proliferation capacity, transmission of adhesion molecules, growth factors and receptors in the tumour. Furthermore, expression of somatostatin receptors and induction of the enzyme 2'-5'-A-synthetase may guide the treatment.

To summarize, a greater awareness of neuroendocrine gut and pancreatic tumours has emerged among physicians worldwide. Improved histopathological and biochemical diagnosis with chromogranin A and localization procedures such as octreoscan® and endoscopic ultrasound have provided a breakthrough in the clinical work-up. It is hoped that in the next decade these tumours will be diagnosed earlier and that by then surgical cure will more frequently be effected. The medical treatment has significantly improved during the past decade with the introduction of somatostatin analogues and alpha-interferons but new combinations of chemotherapeutic drugs have also been of significant benefit. Biological treatment has prolonged survival in patients with extensive disease and, more significantly, improved the quality of their lives.

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