OVERVIEW ARTICLE

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Guidelines for the Management of Gastroenteropancreatic Neuroendocrine Tumours (Including Bronchopulmonary and Thymic Neoplasms)

Part I—General Overview

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The incidence of neuroendocrine tumours of the gastroenteropancreatic system seems to have increased during the past decade. New diagnostic and therapeutic procedures have aroused the interest of physicians, though most see very few cases of such diseases. A group of members of the Nordic Neuroendocrine Tumour Group decided to compile some guidelines to facilitate the diagnosis and treatment of patients with these tumours. Part I of these guidelines discusses the principles of histopathology, biochemical and radiological diagnosis as well as therapeutic options.

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THE NEUROENDOCRINE CELL SYSTEM

The neuroendocrine (NE) cell system consists of nerve cells (with their nerve fibres) and epithelial cells. They synthesize peptide hormones and biogenic amines. The NE nerve cells occur in the brain and the nerve ganglia outside the brain. Their nerve fibres form the large peptidergic and adrenergic autonomic nervous system. The epithelial NE cells form, to a great extent, the parenchyma of the classical endocrine glands. Nevertheless, most of them occur as disseminated cells in the mucosa of the respiratory and alimentary tracts. Basically NE cells can appear in all solid organs and in the skin and all mucous membranes of the body.

Both phylogenetically and ontogenetically, the NE cells originate from the nervous system. The hormonal peptides and biogenic amines are synthesized in the endoplasmatic reticulum of the NE cells, packed in their Golgi apparatus, and stored in secretory granules of the cytoplasm. Via exocytosis, the stored hormones are released to the blood or sometimes intra-luminally in the gut.

The nerve cells of the NE system rarely undergo hyperplasia and/or neoplastic transformation. In contrast, the epithelial NE cells, both those in the endocrine glands and those disseminated in the mucous membranes and the skin, can form hyperplastic tumour-like nodules and genuine neoplastic growths.

As in most other neoplasms of the body, the etiology and pathogenesis are essentially unknown in the NE tumours. However, genetic abnormalities and cell growth aberrations

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due to overstimulation by hormones and growth factors are known to be responsible for the initiation of NE hyperplasias and genuine NE neoplasms. Certain people are predisposed to the tumours due to genetic alterations such as in MEN-I families as well as von Hippel Lindau's disease.

The course of the NE neoplastic diseases varies to a considerable extent. Assessment of the degree of malignancy of individual NE tumours can be difficult. The main tools for this assessment are comprehensive histopathological and immunohistochemical examinations combined with the medical history. In particularly difficult cases, electron microscopy must also be included. Particular attention is being paid to the size of the tumour nodule, its depth of invasion, and the growth pattern of the neoplastic cells, as well as their degree of differentiation and proliferation potency. Both lymphatic and haematogenous spread of metastases can occur in malignant NE neoplasms. Thus, metastatic lesions can appear in most organs and tissues. The predominant pattern is, however, a spread to the regional lymph nodes and, later on, also to the liver, bone, and brain.

The neoplastic parenchymal cells retain their ability to produce peptide hormones and biogenic amines. Thus, also a metastatic NE tumour can give rise to clinical symptoms of hormone overproduction.

The proteins in the secretory granules of virtually all the NE cells predominantly consist of the glycoprotein chromogranin A (CgA) which is secreted into the blood. Thus, when an NE tumour develops, the level of CgA in the blood usually becomes elevated. CgA assessments in the blood can also be used to follow the course of an NE neoplastic disease.

Another common cell-biological feature of NE cells, normal, hyperplastic, and neoplastic ones, is that they often contain somatostatin (and other peptide) receptors on their cell surface. This fact gives opportunities for both scintigraphic diagnosis and therapy. For detailed description of histopathology of different tumour types—see Part II (1).

EPIDEMIOLOGY OF NE TUMOURS

NE gastroenteropancreatic (GEP) tumours constitute less than 2% of all gastrointestinal malignancies. The incidence of the largest group of patients, those with small intestinal carcinoid tumours, is 2.0 to 2.4 per 100 000 inhabitants. The true incidence is probably underestimated due to sometimes vague clinical presentation and low awareness among physicians. The incidence in autopsy series is significantly higher at 8.4/100 000 inhabitants (2).

Although NE tumours can appear at all ages, those of the lung, mediastinum, and gastrointestinal tract are, in general, age-related with the highest incidence from the fifth decade upwards. Exceptions to this are the carcinoids of the appendix, which occur with the highest incidence below 30 years of age, followed by the age group between 30 and 49 years. MEN-1 patients may have a clinical onset 15 years earlier than patients with sporadic cases (3, 4).

MEN-1

MEN-1 is associated with parathyroid hyperplasia/hyperparathyroidism (90%), pancreatic endocrine tumours (non-functional, gastrinomas, insulinomas, glucagonomas) (50–80%), pituitary adenomas (30–40%), adrenal cortical adenomas (10–15%), and also skin fibromas/lipomas, thymic, gastric, and bronchial tumours. The mean age of clinical diagnosis has been reported to be around 30 years. However, in screened families it is about 15 years. No exact figures for incidence are available, whereas a prevalence of 0.2 has been reported. It is a general belief that MEN-1 is largely under-diagnosed in most countries (4).

A specific deletion on chromosome 11q13, harbouring the MEN I-gene, is the genetic background of the disease. This gene encodes a protein called menin, which acts as a tumour suppressor (5, 6).

According to the lower age of onset of parathyroid disease, symptoms related to hypercalcemia are most frequently the first presentation of disease. During later

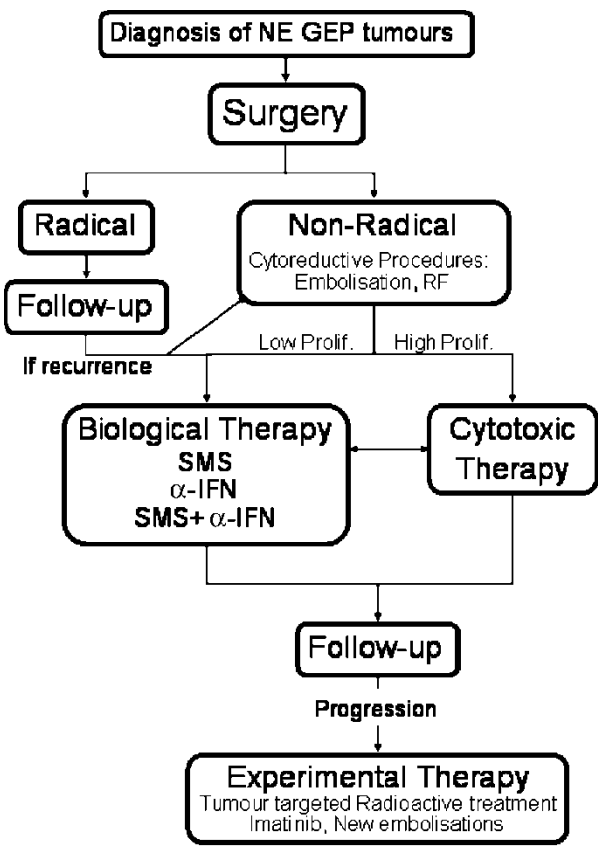

Fig. 1. Suggested algorithm for treatment of NE tumours. The tumour-targeted radioactive treatment has been placed in the experimental therapy column but with future development of this treatment it could be placed higher up in the algorithm, directly after non-radical surgery.

stages of disease, symptoms and signs are related to localization, size, and hormone activity of the tumours of the affected person. This might be related to local symptoms of the pituitary gland, local compression in the mediastinum or lung, or hormonal activity as well as local/regional or liver metastases from a pancreatic tumour. The most common clinical syndrome associated with MEN-1 and pancreatic or duodenal NE tumour is Zollinger–Ellison syndrome (40%). Other clinical syndromes include hypoglycaemia (20%), VIPoma syndrome (2–5%), and glucagonoma syndrome (1–2%). Most tumours are initially non-functioning. Genetic screening for MEN-1 should be offered to family members. Those with genetic deletion should be followed up annually for detection of parathyroid disease, pituitary, pancreatic, and other tumours (4, 7).

NEUROFIBROMATOSIS TYPE 1—VON HIPPEL LINDAU'S DISEASE

The von Hippel Lindau's (VHL) syndrome is an autosomal-dominant neoplastic syndrome characterized by hemangioablastomas of the central nervous system, retinal angiomas, renal cell carcinomas, pheochromocytomas, and NE pancreatic tumours. More than 90% of gene carriers express one or more of the manifestations of this disorder by the age of 60 years. Although the tumours may immunostain weakly for insulin, they virtually never hypersecrete. The VHL gene was mapped to chromosome 3p25.3 and identified by positional cloning. This gene is a tumour suppressor gene, implying that loss of function or inactivating mutations of this gene are associated with tumour formation (8, 9).

Neurofibromatosis type 1 (NF-1)

The main features of NF-1 are neurofibromas and café-au-lait spots. NF-1 has been associated with a variety of endocrine neoplasms, including pheochromocytoma, hyperparathyroidism, somatostatin-producing carcinoid tumours of the duodenum, and medullary thyroid carcinoma. The causative gene for NF-1 encodes a GTP- activating protein named neurofibromin which accelerates GTP-1 hydrolysis of p21. Loss of the GTP's activating function of neurofibromin leads to p21 ras-activation (10, 11).

Diagnostic procedures

Histopathology. Biopsy material, preferrably surgical or coarse-needle biopsy specimens, is conventionally fixed in formalin and paraffin-embedded; specimens for EM are fixed in glutaraldehyde and embedded in Epon. Fine needle aspiration (FNA) biopsy material can also be used, mostly for supporting an initial clinical diagnosis of an NE tumour (see below).

Only conventional light-microscopical tinctorial procedures are usually needed for visualizing the NE neoplastic cells and their characteristic growth pattern. Most pathologists immediately recognize some of the classical carcinoid growth patterns; the insular (Type A), the trabecular (Type B), the glandular (Type C), and/or the undifferentiated (Type D) ones. Likewise, the NE tumours of the pancreas are, as a rule, easily recognized in routine diagnostic histopathological examinations, as well as the small-cell ('oat-cell') carcinomas.

Notwithstanding, immunohistochemical (IHC) analyses nowadays form the basis for a more exact histopathological diagnosis. The IHC analyses are primarily directed towards those biogenic amines and neurohormonal peptides that are characteristic for the NE organ from which the tumour has arisen. The most commonly used general IHC markers for NE tumours are CgA and synaptophysin, which are related to the hormone storage in the classical NE secretory granules (large, dense-core vesicles) and in the small, synaptic-like vesicles, respectively. In poorly granulated NE cells, their NE nature can become IHC visualized by means of their cytosol antigens, mainly neuronspecific enolase (NSE) and PGP 9.5.

It is well known that both conventional tumour-pathology criteria and the results of DNA cytometry are of limited value in the assessment of the degree of malignancy of an NE tumour. Therefore, an IHC analysis of the proliferation potential of the neoplastic NE cells has become a more or less compulsory technique. It is usually performed by means of the MIB-1 antiserum to the Ki-67 proliferation antigen, resulting in a 'Proliferation Index' (PI) of the neoplastic parenchyma. A simple counting of mitotic figures per 10 high-power fields (HPF) in the light-microscope is an alternative procedure for creating a PI.

IHC analyses of the presence of various somatostatin receptors on the cell membranes of the neoplastic NE parenchymal cells have still not become an established routine technique in histopathological laboratories.

FNA biopsies can reveal the presence of granulated neoplastic cells, possibly of NE nature. However, for natural reasons, the FNA specimens often fail in the subsequent efforts to make any more detailed diagnosis of the NE tumour, in particular with regard to its growth pattern and its Ki-67 IR.

EM examinations are needed only in those cases where the neoplastic parenchyma is so poorly differentiated that the IHC analyses are not sensible enough to disclose the NE features. Then, in the EM, it can ultimately be decided whether or not characteristic NE secretion granules and/or the synaptic-like vesicles are present in their cytoplasm.

An optional technique—for instance to be used in cases of poorly differentiated NE carcinomas—is to increase the sensitivity of the IHC procedure by means of the TSA (Tyramide Signal Amplification) procedure. However, it is still not a method available routinely in histopathology laboratories (12–15).

The new (WHO) classification system. In the year 2000, the WHO revised the histopathologic classification system of GEP NE tumours. Then, it was decided that the almost 100-year-old concept 'carcinoid' is no longer adequate to cover the entire structural and biological spectrum of the neoplasms of the disseminated NE system. Instead, the general terms 'NE tumour' and 'NE carcinoma' were introduced. Based on a combination of the classical gross and microscopic structural criteria and the value of the IHC Ki-67 proliferation index (P1) (or the conventional mitotic index), benign NE tumours are distinguished from those with uncertain malignant potential and from NE neoplasms displaying low-grade and high-grade malignancy, i.e. highly and poorly differentiatied NE carcinomas, respectively.

Thus, for the GEP NE neoplasms, they should now be classified as:

- Well differentiated endocrine tumour (PI <2%).
- Well differentiated endocrine carcinoma (PI >2% but <15%).
- Poorly differentiated endocrine carcinoma (PI >15%).
- Mixed exocrine-endocrine tumours.
- Tumour-like lesions.

As a rule, an NE tumour belonging to group 1 shows all the classical structural features of a benign neoplasm. It is small (<2 cm), well delineated, mostly restricted to the mucosa and the submucosa, displaying no angioinvasion, and composed of highly differentiated NE cells with a PI <2%. Typical examples are an enterochromaffin-like (ECL) cell carcinoid in the stomach in a patient with hypergastrinæmia, a classical carcinoid in the tip of the appendix, an incidentally detected trabecular carcinoid of the lower rectum, some ileal 'classical' carcinoids and an insulin-producing NE adenoma of the pancreas.

The neoplastic lesions of a group 2 NE carcinoma are usually larger than 2 cm, displaying widely invasive growth, often also angioinvasion, but still composed of highly differentiated NE cells, with a PI only slightly above 2% (but never higher than 15%). Typical examples are an ileal carcinoid, when discovered by means of its clinical symptoms, and gastrin-producing tumours in the duodenum or the pancreas.

The NE tumours of group 3 represent a neoplasm with all the characteristic features of a highly malignant carcinoma, being large with extensive angioinvasion (and metastases), and composed of neoplastic NE cells, displaying severe atypia and a PI high above 15%. Typical examples are the small-cell ('oat-cell') carcinomas of the bronchi which, exceptionally, also can appear as primary tumours in the lower oesophagus and the colon (16, 17).

Biochemistry. To establish the diagnosis of an NE tumour the demonstration of elevated levels of peptides and biogenic amines in the circulating blood is essential. Plasma CgA is a general tumour marker which is increased in nearly all different types of NE tumours. No clinical symptoms can be related to overproduction of CgA. Other general tumour markers are plasma pancreatic polypeptide (PP) and human chorionic gonadotrophin alfa-subunits (HCGα). For each tumour type characteristic clinical symptoms should lead to measurement of specific markers such as gastrin, insulin, VIP, glucagons, and U-5-HIAA (14).

Radiological imaging. Computer tomography (CT), magnetic resonance imaging (MRI), and ultrasonography (US) detect <50% of NE small gut or pancreatic tumours, but CT and MRI have a higher sensitivity in visualizing NE thymic and bronchial tumours. Approximately 80–90% of liver metastases larger than 1–2 cm are revealed by these radiological techniques. By means of US (and CT) it is possible to take biopsies from tumours and metastases for histopathological evaluation (15).

Endoscopic investigations. Bronchoscopy and thoracoscopy are indicated for identification of bronchopulmonary NE tumours, and mediastinal scopy is relevant for identification of their mediastinal metastases. With all techniques it is possible to take biopsies from tumours and metastases for histopathological evaluation. Gastroscopy or colonoscopy with biopsies are needed for the diagnosis of NE tumours in the upper or lower gastrointestinal tract (stomach, duodenum, upper jejunum, and colon/rectum).

Endoscopic ultrasonography. Endoscopic ultrasonography (EUS) combines the techniques of flexible endoscopy with US, as a US probe is attached to the tip of the scope. Tumours, local tumour invasion, and regional lymph node metastases are identified with a sensitivity and specificity of >80%. Furthermore, it is possible to perform a US guided fine needle aspiration of tumours and regional lymph nodes, which may increase the accuracy (16).

EUS is indicated in patients suspected to have NE thymic, bronchopulmonary, gastro-duodenal, and pancreatic tumours. Rectal NE tumours are evaluated for local invasion and regional lymph node metastases by rectovaginal US examinations with rigid probes.

Somatostatin receptor scintigraphy (SRS). Somatostatin receptor scintigraphy is based on the presence of somatostatin receptors in 80–90% of NE tumours. Tumours expressing somatostatin receptor subtypes 2 and 5 are diagnosed and localized with this method. Tumours lacking these receptors such as benign insulinomas can be negative.

The method is a whole-body investigation and enables staging of the disease and, hence, can guide clinicians in therapeutic decisions. The method should always include SPECT and pictures should be taken at 24 (and 48) hours (17).

Positron emission tomography (PET). PET is a functional imaging technique, which can reflect tumour metabolism. Short-lived positron emitting isotopes such as 18F (t½–2h) and 11C (20 min) are used to label substances of

interest. 18F-deoxyglucose (FDG-PET) is being used as an imaging procedure in common cancer, reflecting increased metabolism of glucose in the tumours.

Unfortunately, highly differentiated NE tumours do not show increased uptake of FDG. A specific tracer, 5-hydroxytryptophan (5-HTP), a serotonin precursor, has been labelled with ^{11}C and recent studies have shown increased uptake of ^{11}C-5HTP in NE tumours. The method is more sensitive than SRS and CT in detecting small NE tumours. ^{18}F-L-dopa might be an alternative tracer (18).

Therapy

Surgery. Resection of the NE tumours is the only means of cure in patients with NE tumours. However, cytoreductive procedures have been a major cornerstone in the treatment of malignant NE tumours. In 1960 and 1970 most surgeons were very reluctant to operate on patients with widely metastatic disease but recent development in medical treatment have indicated a need for debulking and bypassing procedures, facilitating the medical treatment. Furthermore, new hormone-blocking agents (somatostatin analogues) have also facilitated the surgical procedure and reduced the risk of carcinoid crises and other severe events. Today, more aggressive surgery has emerged with debulking, laser treatment of metastases, radiofrequency ablation, and also embolization of liver metastases, either as plain embolization or combined with cytotoxic agents. A patient with an NE tumour should be discussed with a surgeon to establish a fruitful collaboration and to decide when, during the course of the disease, surgery might be most beneficial (19)

Management of liver metastases. In patients with liver metastases, surgical treatment of the primary NE tumour is recommended. Surgery for liver metastases is indicated for curative intent, as well as for palliation. Severe hormone-related symptoms (e.g. carcinoid syndrome, hypoglycaemia), which could not be controlled by medical therapy and improvement of medical therapy, are indications for surgery of liver metastases.

Depending on the location of the liver metastases, the following surgical approaches are used: atypical liver resection (enucleation), one or more segmental resections, hemi-hepatectomy, and extended hemihepatectomy, involving segments of both liver lobes. Surgical resections may be combined with other ablation techniques, particularly with radio-frequency ablation. Surgery for liver metastases should always include intraoperative US for detection of all metastases and of the relation to the major intra- and extrahepatic vessels and bile ducts.

In patients with multiple liver metastases, there are several options: debulking surgery, radiofrequency ablation, cryoablation, laser therapy, radiological (chemo) embolization, medical therapy, or combinations of these. Surgical dearterilization is not recommended. The treatment selected has to be designed individually for each patient (20, 21).

When considering surgical treatment for liver metastases, it should be emphasized that the treatment should never be more dangerous for the patient than the disease itself.

Embolization of liver metastases. Selective embolization alone or in combination with interarterial chemotherapy (chemoembolization) is a widely performed procedure to reduce clinical symptoms, as well as liver metastases. Selective embolization of peripheral arteries induces temporary ischemia. The procedure can be performed repeatedly. The objective response rates have varied between 30% and 70% significant tumour reduction. Chemoembolization consists of intra-arterial injection of a cytotoxic drug together with embolization material. The local drug concentration may be 20 times higher than that achieved by systemic intravenous injection. The cytotoxic agents most often used are 5-FU, doxorubicin, or mitomycin C. Chemical responses have been reported in 70–90% of patients and significant tumour reduction in 30–50% of patients. The duration of symptomatic response has been reported to be 15–30 months. Minor side effects of embolization and chemoembolization are postembolization syndrome with nausea, right upper quadrant pain, fever, and elevation of liver transaminases. Major side effects are gallbladder necrosis, hepato-renal syndrome, pancreatitis, and liver abscess. The mortality of the procedure might be as high as 7%. Details of this procedure are still not clear, e.g. the timing of sequential chemoembolization and choice of cytotoxic drugs. Whether imaging offers a reliable modality for evaluating the efficacy of chemoembolization is a matter of debate as differentiation of viable from non-viable tissue may be difficult (22).

Liver transplantation may be considered in young patients in whom all extrahepatic tumours and metastases are previously removed and follow-up does not visualize recurrence of extrahepatic tumour tissue. About 400 transplantations have been performed worldwide, so far. However, practically all patients have developed recurrence within months to years later. It is still to be clarified which patients benefit from transplantation, taking into account the risk of operation and postoperative immunosuppressive therapy. Liver transplantation should not be performed in patients subjected to a previous Whipple's procedure (23).

Somatostatin analogues. The somatostatin analogue octreotide has been in clinical use for treatment of NE tumours since the early 1980s. Somatostatin analogues are synthetic somatostatin octapeptide derivatives with structure and activities similar to those of the native hormone somatostatin, containing 14 amino acids, but with a significantly longer half-life and duration of action than the native substance (24).

Mechanism of action. Somatostatin can exert both cytotoxic and cytostatic actions. It mediates cell cycle arrest at

the G1 phase and the effect of somatostatin analogues is mediated through somatostatin receptor subtypes 2 and 5, and to a smaller degree type 3. They inhibit the release of peptides from the tumours and thereby improve clinical symptoms related to these peptides. Somatostatin also exerts receptor-independent effects to influence cell growth, including endocrine effects, inhibition of angiogenesis, and effects on the immune system. Somatostatin analogues can induce apoptosis, particularly at high doses (25, 26).

Preparations. Octreotide and lanreotide are clinically available somatostatin analogues. There are both short-acting and long-acting formulations of octreotide (Sandostatin LAR®); lanreotide is available only in a slow-release formulation (Lanreotide-PR and Somatuline Autogel®) (27, 28).

Dosages. Standard doses for short-acting octreotide are 100 to 500 μg three times daily. The dose of octreotide LAR varies from 10 mg to 30 mg (up to 60 mg) every 4 weeks. The dose of the slow-release lanreotide ranges from 60 mg to 120 mg every 4 week. Changes from short-acting octreotide to octreotide LAR can be made as follows: <500 μg/d short-acting octreotide is changed to 20 mg Sandostatin LAR every 4 weeks, and >500 μg/d to 30 mg, respectively. Short-acting octreotide is continued for 2 weeks after starting Sandostatin LAR. Breakthrough events can be treated by short-acting octreotide. Always test the patient's tolerance with short-acting octreotide for 1–2 days before giving a long-acting analogue!.

Prediction of response. Response to treatment with somatostatin analogues can be predicted by somatostatin receptor scintigraphy. There are, however, reports on clinical responses to treatment despite negative scintigraphy.

Efficacy. With octreotide and lanreotide, symptomatic relief is achieved in more than 60% of patients. Biochemical responses are observed in up to 70% of patients. Significant tumour responses in terms of reduction in size ($>50\%$) are seen in 5–10% of patients. In progressive disease, tumour stabilization has been observed in 36–70% of patients, with the duration of stabilization ranging from 2 to 60 (median 12) months. Single patients have been stabilized for 10 years (27, 29).

The efficacy can be improved by adding alfa-interferon (see below). If the patient has not responded to one somatostatin analogue, it is worth trying another preparation. Combination with chemotherapy can be applied.

Octreotide has lengthened survival time in comparison with historical controls and the quality of life has been significantly improved by somatostatin analogues (30).

Indications. Somatostatin analogues are the primary medical treatment for patients with symptoms related to peptide-producing NE tumours. For patients with insulinoma and gastrinoma, these agents can be used as second- or third-line medical treatment. They can also be considered for asymptomatic patients with progressive disease, excluding aggressive tumours. At present, it is controversial as to whether somatostatin analogues should be considered also for asymptomatic patients with stable disease. This will be addressed by further, controlled studies.

Short-acting octreotide is used to treat and avoid carcinoid crisis before, during and after procedures such as surgery and embolization. This relates also to patients on long-acting formulations.

Adverse effects. The most relevant adverse effect is the development of gallstones because of inhibition of cholecystokinin release, which postprandially induces emptying of the gallbladder. Up to 60% of patients under long-term treatment may develop sludge in the gallbladder but less than 10% clinically significant gallstones. Nausea, flatulence, abdominal pain, diarrhoea, and steatorrhoea may occur due to inhibition of gastrointestinal physiological function. Many patients benefit from substitution of pancreatic enzymes. Other rare adverse events include pain at injection site, hypoglycaemia or hyperglycaemia, rash, alopecia, and fluid retention. Adverse effects rarely necessitate discontinuation of treatment (27).

Alpha-interferon (α-IFN). The cytokine alpha interferon was introduced in the therapy of midgut carcinoids in the early 1980s. It was noted that midgut carcinoid patients had somewhat low natural killer cell function compared with healthy blood donors. α-IFN was at the time the only known compound that could stimulate NK-cell activity (31).

Mechanism of action. α-IFN exerts a direct effect on the tumour cells by blocking the cell cycle in the G1/S-phase, by inhibiting protein and hormone synthesis, and by anti-angiogenesis through inhibition of angiogenic factors, b-FGF and VEGF, and their receptors. It also has an indirect effect through stimulation of the immune system, particularly T-cells, NK-cells, macrophages, and monocytes (32–34).

Preparations. Today, recombinant α-IFNs are available (Intron-A®, Roferon®) Pegylated interferons are long-acting formulations (Peg-Introna®, Pegasys®). Multiferon®, a human leucocyte IFN is also available.

Dosages. The dose should be individually titrated in each patient. The leucocyte count could be of some guidance, aiming at a reduction of the blood leucocyte count to about 3.0^9/l. Usually, the dose of regular α-IFN should be 3–5 million units (MU) 3–5 times per week subcutaneously. The precise dose of pegylated α-IFN has still to be established in forthcoming studies but doses of 75–150 μg per week subcutaneously could be feasible (32).

Prediction of response. Response to α-IFN can be predicted by analysing induction of 2,5-oligoadenylate synthetase or P68(PKR) protein kinase, enzymes involved in cell cycle regulation and protein synthesis. However, these methods are not available in clinical practice (32).

Efficacy. The average response rates according to WHO criteria are: Symptomatic responses 40–60%, biochemical 30–60%, tumour reduction 10–15%. Tumour stabilization is noted in 40–60% of patients with midgut carcinoids, lasting for long periods of time (more than 36 months). Single patients have been stabilized for 10–15 years (32).

Indications. α-IFN can be considered as primary medical treatment for low-proliferating NE GEP tumours with or without syndrome, either alone or in combination with somatostatin analogues. It could be attempted as second-line therapy after cytotoxic treatment alone or in combination with somatostatin analogues. Approved indications vary between different countries (32).

Combination therapy. Combinations of α-IFN with somatostatin analogues have generated additive and also possibly synergistic effects in the treatment of classical carcinoids and NE pancreatic tumours. α-IFN is known to upregulate the expression of somatostatin receptors, and somatostatin analogues reduce the side effects of α-IFN. However, the frequency of significant tumour shrinkage has not increased using this combination of drugs. Other combinations of α-IFN and cytotoxic agents (5-FU, doxorubicin) have not generated increased response rates but significant toxicity has been noted (33, 37, 38).

Adverse effects. α-IFN is a potent cytokine with multiple intracellular actions. Most patients experience flu-like symptoms and fever during the first week of treatment. The most severe and dose-limiting toxicity is the chronic fatigue (in 30–75% of patients), mental depression (in 5–10% of patients), and neurological disorders (in 5–10% of patients). Other side effects are anaemia, leucopenia, thrombocytopenia, and increased liver enzymes in 10–30% of the patients. Severe side effects might be development of myositis and SLE-syndrome, which necessitate withdrawal of the therapy. Other autoimmune reactions, such as autoimmune thyroiditis, can be managed by standard endocrine procedures, including therapy and laboratory measurements. Autoimmune hepatitis, psoriasis, SLE, rheumatoid arthritis, and dementia are contraindications (32, 33).

Chemotherapy. Cytotoxic treatment has been the gold standard for most NE tumours over the last three decades. However, the increasing awareness that low-proliferating NE tumours respond very poorly to cytotoxic treatment has stimulated the development of new biological treatments for slowly progressing NE tumours. Cytotoxic treatment is still to be considered as first-line treatment for high-proliferating tumours, i.e. metastatic disease with angio-invasion and proliferation index above 10%. Single-agent cytotoxic treatment has been of limited value in most trials producing response rates of less than 30%. The combination of streptozotocin (STZ) plus 5-FU and doxorubicin has shown response rates of more than 50% in malignant NE pancreatic tumours with a median duration of more than 2 years. Malignant pulmonary NE tumours, as well as colorectal carcinoids, respond poorly to this combination, as do the classical midgut carcinoids. Poorly differentiated NE tumours, particularly foregut (pulmonary, thymic) and small-cell colorectal NE tumours, might respond to a combination of cisplatinum/paraplatin plus etoposide. These tumours present a high-proliferation capacity, i.e. more than 15% Ki67 IR cells. The response rate has been reported to be 60–70% in poorly differentiated NE tumours with a duration of 8–9 months. Well-differentiated malignant tumours do not respond to this combination (33, 39–41).

Mechanism of action. STZ, as well as 5-FU, cisplatinum, paraplatinum, and etoposide, are all cytotoxic agents and exert their anti-tumour effect via damage of cellular DNA.

Dosages. There are many different cytotoxic schemes worldwide and no one has proved to be significantly better than the others. STZ plus 5-FU is usually administrated by bolus injections with an induction course of 5 days of STZ 1g/day intravenously for 5 days combined with 5-FU 400 mg/m^2 on days one to three, i.e. short infusion. After this initial course STZ 2 g and 5-FU 400 mg/m^2 are given intravenously during one day every 3 weeks until toxicity. When doxorubicin is combined with STZ, 40 mg/m^2, it is given on day three. One or two years after stabilization of the tumour growth the interval between the courses may be increased to 4–6 weeks. For cisplatinum/paraplatinum, and etoposide, there are several different schemes and we refer to standard oncology textbooks for dosing.

Prediction of response. There are no predictors of response during treatment with cytotoxic agents. Biochemical markers can be of value, but usually one has to wait for at least 2–4 weeks until a significant drop in biochemical markers can be noticed.

Efficacy. The average response rates according to WHO criteria for STZ plus 5-FU is about 50–60% in patients with NE pancreatic tumours. For other types of NE tumours, the response rates are significantly lower in the range of 25–30%. For cisplatinum plus etoposide, the response rates in poorly differentiated NE carcinoma are about 55–60% with a duration of 8–9 months. For well differentiated NE tumours the response rates are significantly lower in the range of 10–15% with a median duration of 6 months (33, 42).

Indications. Cytotoxic treatment could be considered as first-line treatment for malignant NE tumours in the pancreas and also for gastric carcinoids, provided that the PI is $>10\%$. It could also be considered as second-line treatment, after failure of other means of treatment such as biological treatment in foregut and midgut carcinoids, and after tumour-targeted radioactive treatment.

Combination therapy. A combination of cytotoxic treatment with somatostatin analogues is recommended in patients with clinical syndromes related to hormone

overproduction. The addition of somatostatin analogues improves the clinical symptoms and also prevents the development of severe attacks related to release of vasoactive substances during the development of necrosis of NE tumours.

Adverse effects. Adverse effects of the combination of STZ plus 5-FU or doxorubicin include nausea, vomiting, and renal toxicity; with doxorubicin also alopecia. Antiemetics such as 5HT3-receptor blockers can control nausea in 80–90% of patients. Nephrotoxicity is the dose-limiting toxicity. The combination of cisplatinum plus etoposide is accompanied by significant toxicity, including alopecia, nausea, vomiting, bone marrow and renal toxicity, and neuropathy. The combination of carboplatin and etoposide may be less toxic but the efficacy is not yet evaluated (33, 40, 42).

Radiation therapy. NE tumours are considered to be relatively radio-resistant. Conventional external radiation therapy is recommended only for bone and brain metastases. Tumour-targeted radioactive treatment with ^{111}Indium DOTA octreotide or ^{90}Yttrium DOTA octreotide, and ^{177}Lutetium DOTA octreotate has generated significant interest during the last few years. The response rates with standard WHO criteria reported have been around 20–25% significant tumour shrinkage, with biochemical and clinical responses in 40–50%. The precise role of tumour-targeted radioactive treatment is not yet defined but future randomized trials will give us more information on how to use this kind of treatment. ^{131}IMIBG has been attempted, mainly in classical midgut carcinoids, with some beneficial effect with biochemical responses in 30–40% of the patients and tumour responses in about 20%. This treatment may be replaced in the near future by the somatostatin analogue based tumour targeted radioactive treatment (43–45).

New agents. There is rapid development of new agents in general oncology and some of these agents might be also attempted in NE tumours. It is well known that a significant number of NE tumours express tyrosine kinase receptors, such as PDGF-alfa and -beta receptors, C-kit, and EGF receptors. New agents, such as Imatinib, but also other tyrosine kinase inhibitors, might be of beneficial value in selected patients. Many NE tumours are highly vascularized and, therefore, the blood supply might be the target for new anticancer treatment in NE tumours. A number of new antiangiogenic substances will be attempted in NE tumours such as endostatin, angostatin, and the new compound ZD6126. Rapamycin, a compound initially developed to prevent rejection after organ transplantation, has shown in vitro effects in NE cell-lines with inhibition of proliferation and induction of apoptosis. New somatostatin analogues are to be tested in NE tumours, such as SOM230, which binds, for example, to somatostatin receptors 1, 2, 3, and 5; they have demonstrated a significant inhibitory effect on the product of various hormones, not only growth hormone but also IGF-1. This analogue will be tested in forthcoming clinical trials in the near future. Somatostatin receptor subtype specific analogues may be tested in the future and, with the development of specific analogues to different somatostatin receptors, custom-made somatostatin analogue treatment can be provided in patients with NE tumours.

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