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Review paper

Endocrine tumors of the gastrointestinal tract: systemic treatment

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Neuroendocrine gut and pancreatic tumors are neoplasms that present distinct features from other malignant tumors. Firstly, in most patients, tumor growth is rather slow, and even in advanced metastatic disease, there is very little impairment of the general well-being of the individual, e.g. appetite and weight. Secondly, these tumors are known to produce specific peptide hormones which may be factors in some clinical conditions e.g. carcinoid, Zollinger–Ellison and hypoglycemic syndromes. These conditions can be critical to the patients and can occasionally be lethal. Therefore, the treatment of neuroendocrine tumors must control the clinical symptoms related to hormone over-production and prevent further tumor growth. These two features are not always in parallel. Systemic treatment of neuroendocrine tumors mainly consists of chemotherapy, interferon and somatostatin analog administration. Chemotherapy has been used for at least 30 years; the most effective combination has proved to be streptozotocin with 5-fluorouracil or adriamycin. This combination produces biochemical responses in up to 60% of patients with endocrine pancreatic tumors; the results in carcinoid patients are very poor and response rates are ≤10%. Alpha-interferon (IFN-α) produces biochemical responses in approximately 50% of patients with malignant carcinoid tumors, significant reductions in tumor size in 15% and a further 39% of patients have disease stabilization with no further tumor growth. Somatostatin analogs have only been used clinically within the last 10 years, but produce symptomatic improvement in 70% of cases, biochemical responses in 40–60%, but rarely produce any significant reduction in tumor size. These analogs are particularly useful to control severe clinical symptoms and are the first-line therapy for the management of carcinoid patients both peri- and intra-operatively. Patients with endocrine pancreatic tumors, particularly those with glucagon and vasointestinal peptide-producing tumors, benefit most from this type of treatment. Recently, a combination of IFN-α and a somatostatin analog has showed an additive effect of these two drugs. The side effects of streptozotocin and 5-fluorouracil are mainly nausea and vomiting which can be controlled with 5-HT_3 receptor blocker therapy. Another significant adverse reaction is impaired renal function. The adverse reactions to IFN-α are mainly flu-like symptoms, fatigue, mild impairment of liver and bone marrow function and autoimmune reactions in 15% cases. Somatostatin analog treatment causes a low frequency of adverse reactions, those which do occur include gall stone formation and steatorrhea. Future systemic treatment should be based on increased knowledge of the tumor biology, particularly growth-regulatory mechanisms. At present, the majority of treatment is to control the disease. Therapies to cure patients with advanced stages of neuroendocrine tumors have yet to be established.

Key words: Carcinoid tumors, chemotherapy, doxorubicin, endocrine pancreatic tumors, 5-fluorouracil, interferon-α, neuroendocrine tumors, somatostatin analog, streptozotocin.

Introduction

Neuroendocrine gut and pancreatic tumors (GEP) are rare and constitute about 2% of all malignant gastrointestinal neoplasms. The incidence of patients with malignant tumors and the carcinoid syndrome is around 0.5 per 100 000 and with endocrine pancreatic tumors 0.4 per 100 000.[1,2] A majority of patients with malignant metastasizing tumors demonstrate clinical symptoms related to hormone overproduction. These syndromes include the carcinoid syndrome with flushing, diarrhea, bronchial constriction, right heart failure due to classical midgut carcinoids with production of serotonin and tachykinins.[1] Syndromes related to endocrine pancreatic tumors are the Zollinger–Ellison syndrome due to gastrin overproduction, insulinoma or hypoglycemic syndrome because of insulin/proinsulin overproduction. Other distinct clinical entities are the glucagonoma syndrome including the typical necrolytic migratory erythema due to glucagon production, the Verner–Morrison syndrome because of high circulating levels of vasoactive intestinal peptide (VIP) giving severe secretory diarrhea with various degrees of electrolyte disturbances, and, finally, somatostatinoma, a syndrome with gall bladder dysfunction, gall stones, steatorrhea and impaired glucose tolerance.[2]

Carcinoid tumors can be devided into three main groups; foregut, midgut and hindgut tumors. Pri-

mary lesions of the 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, cecum and proximal colon (50–70%). Appendix carcinoids are predominantly benign and rarely present metastatic disease. The hindgut tumors are primarily located in the distal colon and rectum, and they constitute the second most common type (15–20%) of all carcinoids. The midgut carcinoids are mainly present in material of malignant carcinoid tumors and particularly in the case of the carcinoid syndrome (flushing, diarrhea, bronchial constriction and right heart failure).[1,3,4]

About one-third of patients with endocrine pancreatic tumors present without any hormone related clinical syndromes. In addition, neuroendocrine tumors of the hindgut area (colorectal carcinoids) do not usually present any peptide hormone related syndromes.[3] Even in advanced stages, tumors with metastases demonstrate a high degree of differentiation with primarily diploid DNA features.[3] The hormone production and release with related metabolic consequences may sometimes be life-threatening even in patients with rather small tumors and limited metastatic spread. About one-third of the patients with carcinoid syndrome die from carcinoid heart disease and not from tumor growth.[1] Therefore, even if the tumor itself is advancing slowly, the hormone overproduction might be devastating to the patient, resulting in a reduced quality of life.

Because of the tumors' rarity, their sometimes episodic expression and diffuse clinical symptoms, patients are diagnosed relatively late in advanced stages of the disease. Endocrine gut and pancreatic tumors have been assigned a good prognosis, and therefore many physicians have been reluctant to administer medical treatment in early stages of the disease. A critical look at 5 year survival rates in patients with malignant neuroendocrine tumors, however, demonstrates survival rates of less than 20% when liver metastases are present. The median survival for patients with malignant carcinoid tumors and the carcinoid syndrome is reported to be less than 2 years from diagnosis of a carcinoid syndrome.[4,5]

Treatment of neuroendocrine gut and pancreatic tumors always includes surgical considerations. Resection of local disease or resection of regional, nodular metastatic disease can result in a cure in some patients, but even if radical surgery cannot be performed, debulking procedures and by-passing should always be considered and can be performed at any time during the ongoing medical treatment.[6–11] By combining aggressive surgery with medical treatment we have been able to obtain a median survival for patients with the most advanced disease, the malignant carcinoid syndrome and liver metastases occupying more than 50% of the liver mass of almost 5 years (56 months) from start of treatment (to be published).

The role of surgery in the treatment of patients with gastrinomas, Zollinger–Ellison syndrome and the multiple endocrine neoplasia type 1 (MEN 1) syndrome is very much debated. The disease involves the total pancreas with multiple micro- to macro-tumors spread all over the gland.[12] Moreover, more than 40% of the tumors might be located in the duodenal wall besides the pancreatic location.[13] Therefore removal of one or two lesions seldomly results in normal gastrin or other hormone levels.

In general radiation therapy has not been successful in the treatment of metastatic neuroendocrine tumors, except for treatment of symptomatic bone and skin metastases.[14]

Hepatic artery ligation surgically or embolization (Spongostan®, Ivalon®) by interventional radiology has been reported to reduce hepatic tumor bulk.[5,15,16] 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 less than 12 months. The combination of hepatic artery ligation and combination chemotherapy with dacarbazine, doxorubicin, 5-fluorouracil (5-FU) and streptozotocin has led to dramatic response rates in patients with neuroendocrine tumors and hepatic metastases. Recently Moertel and co-workers have put together their data on 111 patients with advanced carcinoids and islet cell tumors who were subjected to hepatic artery occlusion done surgically or by embolization. After this procedure, 71 patients were selected for chemotherapy with alternating two-drug regimens of doxorubicin plus dacarbazine and streptozotocin plus fluorouracil. Objective regressions were observed in 60% of patients treated with occlusion alone and in 80% when chemotherapy was added. The median duration of regression was 4 and 18 months, respectively, and the side effects were tolerable.[17]

Chemotherapy of neuroendocrine gut and pancreatic tumors

Chemotherapy of carcinoids and endocrine pan-

creatic tumors has frequently been reported in a very sketchy fashion; these studies generally involving only a limited number of cases with various criteria for assessing antitumor responses. Furthermore, many studies do not take into consideration the different biological behavior between 'classical' midgut carcinoids and endocrine pancreatic tumors, so that sometimes both types are evaluated together in the same study. It is essential to review the chemotherapeutic data individually for the various neuroendocrine tumors.

Single-agent chemotherapy in malignant carcinoid tumors

The overall results are summarized in Table 1. The vast experience of single-agent treatment of malignant carcinoid tumors is obtained from studies by Moertel and colleagues at the Mayo Clinic and by the Eastern Cooperative Oncology Group. In their series, 19 patients have been treated with 5-FU 500 mg/m^2/day in 5 day courses given every 5 weeks; they observed five objective responses (26%). In another study by the Eastern Cooperative Group using the same dose and schedule in 11 patients 18% objective responses were noticed.[6,18]

Two separate trials applying doxorubicin at a dose of 60 mg/m^2 every 3–4 weeks have reported objective responses in 21% of the patients. Similar results in both studies including 114 patients in total.[18,19] Dacarbazine gave an objective response in three (17%) of 18 treated patients.[38] Actinomycin D has previously been reported to be of value in the treatment of patients with carcinoid tumors, with three out of five patients responding. In a more recent study the result was less encouraging with only one out of 17 patients showing an objective response (5%).[20] Cisplatin has been applied in 15 patients with metastatic carcinoid tumors at doses of 45–90 mg/m^2 by rapid intravenous infusion repeated every 3–4 weeks; only one patient (7%) showed a short lasting response.[21]

Table 1. Single-agent chemotherapy for carcinoid tumors

Agent	No. of patients	Objective response		Reference
		no. of patients	rate (%)	
Streptozotocin	8	0	0	25
	7	1	14	24
	6	1	17	18
Doxorubicin	33	7	21	18
	81	17	21	29
Fluorouracil	19	5	26	18
	11	2	18	33
Dacarbazine	18	3	17	20
Actinomycin D	17	1	6	20
Cisplatin	15	1	7	21

Streptozotocin (Streptozocin) is an alkylating nitrosourea compound which has been the basis for most combinations of chemotherapeutic regimens in patients with various neuroendocrine gut and pancreatic tumors.[22] The drug was already used by Murray-Lyon and coworkers in 1968[23] for the treatment of malignant insulinoma and has thereafter been applied in a large number of patients with neuroendocrine tumors. Due to the glucose moiety of the drug, which is said to reduce the bone marrow toxicity, increased uptake might occur in the pancreatic islets (causing diabetes in animals) and this could make it suitable for treatment of neuroendocrine tumors. The drug is usually administered intravenously and the two most widely tested dose schedules are 1.5 g/m^2 given at weekly intervals and 0.5 g/m^2 given daily for 5 days every 6 weeks. Another more recent schedule is a dose of 0.5 g/m^2 for 5 days followed by 1 g/m^2 every 3–4 weeks.

Renal dysfunction is the major dose-limiting toxic effect of streptozocin and occurs in 20–75% of the patients.[22] The incidence of renal toxicity increases with prolonged drug administration and also depends on scheduling. Manifestations of nephrotoxicity involve abnormalities of both glomerular and tubular function. Protein excretion of more than 500 mg/24 h is a practical limit when the dose should be postponed until the protein excretion falls below this limit. Another serious advent is vomiting occurring in more than 90% of the patients beginning 1–4 h after administration. For about 10% of the patients the vomiting can be so severe and protracted that the treatment has to be stopped. Nowadays, with the introduction of 5-HT$_3$ blockers there has been a renewed interest in treatment with streptozocin, cisplatin or other cytotoxic drugs which would otherwise cause severe vomiting. It is believed that the vomiting is caused by metabolites of streptozocin acting on brain centers.[22] Bone marrow depression is very rare with leukopenia and thrombocytopenia in only 9% of the patients. It is important to realize that when streptozocin is combined with doxorubicin the half-life of doxorubicin is significantly prolonged and the dose of doxorubicin should be reduced compared with the single-agent treatment. Impaired glucose tolerance is very

rarely found in patients treated with streptozocin despite its diabetic action in animals. Other rare adverse effects are elevated liver enzymes, cardiac arrhythmia, CNS-toxicity with mental confusion, depression, skin necrosis and diarrhea.[22]

Streptozocin has been used as single agent in a limited number of patients with carcinoid tumors. In a study by Moertel an objective response was obtained in one out of six patients, and we obtained in one case a short-lasting response out of seven treated patients. Schein and co-workers did not notice any response among eight patients.[18,24,25]

In summary, single-agent chemotherapy of malignant carcinoid tumors has not demonstrated any significant beneficial value in clinical practise. The overall response rates have been low and considerable adverse reactions have been encountered. The duration of responses have been short-lasting, generally less than 6 months. However, there are also isolated cases of patients reported in the literature with long-lasting responses from both actinomycin D and dacarbazine.[21]

Combination chemotherapy for malignant carcinoid tumors

Many different combinations of chemotherapeutic drugs have been tried in malignant carcinoid tumor patients. In the early 1970s, a combination of cyclophosphamide and methotrexate was considered to be the golden rule with almost 50% response rates, but later studies have not been able to confirm these results.[26] During the late 1970s and early 1980s streptozocin based combination regimens were applied in most studies and the results are summarized in Table 2. The overall response rates of these combination trials have varied between 9 and 40% with the largest group of patients treated with a combination of streptozocin and 5-FU giving objective responses in a median of 23% of the patients. The basic principle for combination treatment with streptozotocin has been intravenous infusion of 0.5 g/m^2/day for five consecutive days repeated every 6 weeks. Combined either with 5-FU at a dose of 400 mg/m^2 given daily for five consecutive days and repeated every 6 weeks or cyclophosphamide single dose of 1000 mg/m^2 repeated every 3 weeks. When cisplatin is added the dose has varied from 45 to 90 mg/m^2 given every 3–4 weeks as a bolus injection.[18,19,27–33]

More recently, combination treatments with three or four different chemotherapeutic drugs have been reported for treatment of patients with malignant carcinoid tumor. Streptozocin given at 0.5 g/m^2 for 5 days every 4 weeks combined with 5-FU 500 mg/m^2 for 5 days every 4 weeks and cisplatin 90 mg/m^2 every 3–4 weeks did not improve the response rates in two studies. Neither did a combination of VP-16 130 mg/m^2 for 3 days every 4 weeks combined with cisplatin 45 mg/m^2 for 2 days and the cycles repeated every 4 weeks. No objective response was noticed in 13 patients with carcinoid tumors; however, in 18 anaplastic neuroendocrine tumors 67% objective responses were observed. In a recent study a combination of interferon (IFN)-α 3 MU × III/week subcutaneously, streptozocin 2 g/3 weeks and doxorubicin 40 mg/m^2/3 weeks did not generate any objective responses in 11 patients with malignant carcinoid tumors.[18,32,34–36]

To summarize, no combination chemotherapy trial has so far generated any significant beneficial effect in patients with malignant carcinoid tumors and the carcinoid syndrome. The low response rates of 9–30% are not translated into any prolonged action or survival. In our own study the median survival from start of treatment is only 8 months with chemotherapy (streptozocin plus 5-FU); this agrees with the study by Moertel and colleagues.[19] Similar survival data for somatostatin analogs and IFNs are 36 and 80 months, respectively.[37,38] Therefore, we are still waiting for more effective chemotherapeutic drugs and new combinations for patients with malignant carcinoid tumors.

Table 2. Combination chemotherapy trial in carcinoid tumors

Agent	No. of patients	Objective response		Reference
		no. of patients	rate (%)	
STZ + 5-FU	43	14	33	43
	80	18	23	19
	24	2	8	24
	10	4	40	31
STZ + CTX	47	12	26	32
STZ + DOX	10	4	40	31
STZ + CTX + DOX	20	7	35	27
5-FU + DOX + DPP + 5-FU	15	2	14	27
EPT + DPP	13	0	0	36
STP + DOX + IFN-α	11	0	0	34

STZ, streptoxotocin; 5-FU, fluorouracil; CTX, cyclophosphamide; DOX, doxorubicin; DPP, cisplatin; ETP, etoposide (VP16).

Chemotherapy of endocrine pancreatic tumors

In clear contrast to the lack of accomplishment of chemotherapy for carcinoids is the sometimes remarkable success for endocrine pancreatic tumors. Streptozocin-based combinations have been the basis for chemotherapy in malignant endocrine pancreatic tumor patients. It was introduced in the clinic for the first time by Murray-Lyon and colleagues[23] in 1968 for treatment of an insulinoma, and subsequently a large series compiled by Broder and Carter from the National Cancer Institute[39] confirmed the activity of streptozocin in pancreatic islet cell cancer. In this series, 37% of the patients with measurable disease had an objective regression and 54% of functional tumors had at least 50% reduction of biochemical markers. There exist several schedules for administration of streptozotocin but none is superior to the other. Some investigations favor administration by a 5 day course (1 g/m^2/day) every 6 weeks, whereas others prefer weekly bolus administrations of 1 g/m^2/day. A third alternative is a 5 day induction course with 0.5 g/m^2/day for 5 days followed by a bolus injection of 1 g/m^2 every 3 weeks. Table 3 summarizes the therapeutic results of chemotherapy in malignant endocrine pancreatic tumors (the most important studies from the 1970s, 1980s and the beginning of the 1990s are listed). Streptozocin alone generates complete and partial remissions in 36–42% of the patients, with a median duration of remission of 17 months and median survival of 1.5 years. Doxorubicin alone generates about 20% partial remissions with a very short duration (median 4 months). In a limited study (10 patients), DTIC induced 50% complete and partial remissions with a very long duration of remission (median 30 months).[28,40–43,47]

Combinations of streptozocin with 5-FU and doxorubicin have been applied in several studies.[59,61,62] The numbers of complete and partial remissions have significantly increased with the combination of streptozocin plus 5-FU varying between 40 and 63%. The duration of remission has varied from 7 to 23 months. The combination of streptozocin and doxorubicin in one study has generated 69% complete and partial remissions with a duration of 18 months and a median survival time of 2.2 years.[44]

Current data clearly indicate that chemotherapy has a significant role in the treatment of malignant endocrine pancreatic tumors with response rates far exceeding those for chemotherapy in malignant carcinoid tumors. However, a critical look at the results from the early 1970s to the early 1990s indicates no significant evolution. The results by Broder in 1973[57] are very much similar to those reported by Eriksson[41] and Moertel in 1992[44] and 1993. The numbers of patients responding to the combination of streptozotocin plus doxorubicin are somewhat higher than those responding to single streptozocin or combination with 5-FU, but this has not led to significantly longer survival. This is further underlined when the two studies by Moertel *et al.* published in 1980[44] and in 1992[45] with similar patients with malignant endocrine pancreatic tumors showed essentially the same results. They could not confirm the response rate for streptozocin plus 5-FU of 63% from 1980 but found only 45% response in the new study. Doxorubicin was significantly more effective with a response rate of 69%, but the survival time and the duration of remission were not significantly longer than in the study in 1980. Therefore, it seems as if combinations of streptozocin plus 5-FU or doxorubicin are almost equally effective and that they are currently the most efficient treatment for endocrine pancreatic tumors giving remissions for almost 2 years and a median survival time of around 2 years. A very promising study was published by Moertel and colleagues in 1991 using a combination of etoposide and cisplatin in patients with very lowly differentiated neuroendocrine tumors.[36] The response rate was as high as 67% for anaplastic tumors with a median duration of regression of 8 months, whereas response rates among well differentiated carcinoid tumors or islet cell carcinomas were only 7%. The median survival for the well differentiated neuroendocrine tumors treated with the same combination was 15 months whereas the anaplastic neuroendocrine carcinoma showed a median survival of 19 months. These data have to be confirmed in forthcoming studies. An important influencing factor in studies of medical treatment of endocrine pancreatic tumors is the type of islet cell tumor which is included. In general, patients with functioning tumors respond better than those with nonfunctioning tumors.[39,41,43,45] Among functioning tumors, insulin- and VIP-producing tumors have been particularly sensitive to streptozocin alone or in combinations.[41]

Chlorozotocin is a new drug which is structurally very similar to streptozotocin; both are nitrosourea compounds.[45] The toxic effects of chlorozotocin include hemathologic depression but with less nausea and vomiting than is associated with streptozocin. The effect of chlorozotocin is similar to streptozocin plus fluorouracil but it produces fewer

Table 3. Chemotherapy for malignant endocrine pancreatic tumors

Reference	Treatment	No. of patients	Treatment results (%) (biochemical and/or tumor responses)					Median remission duration (RD) and survival time (ST) (months)
			CR	PR	CR+PR	SD	PD	
39	STZ 0.6–1.0 g/m^2 weekly	52	20	22	42	25	23	RD: 10+ ST: 42 (CR+PR) ST: 17.5 (SD+PD)
42	DOX 60 mg/m^2 14 weeks	20		20	20	NR	NR	RD: 4 ST: 6
40	DTIC 250 mg/m^2, d 1–5, q 4 weeks	10	10	40	50	20	30	RD: 30 ST: NR
46	STZ 1.5 g/m^2, d 1+d8 5-FU 600 mg/m^2 (gastrinomas) d1+d8 DOX 40 mg/m^2, q 4 weeks	10		40	40		60	RD: 7
41	STZ 0.5 g/m^2, d 1–5 (ind) STZ 1 g/m^2, q 3 weeks DOX 40 mg/m^2, d 3, q 3 weeks	25	4	32	36	40	24	RD: 22 ST: NR
43	STZ 0.5 g/m^2, d 1–5 q 6 weeks	42	12	24	36	NR	NR	RD: 24 (CR) RD: 17 (CR + PR)
	STZ 0.5 g/m^2, d 1–5 q 6 weeks + 5-FU 400 mg/m^2, d 1–5 q 6 weeks	42	33	30	63	NR	NR	ST: 26 (combination) ST: 16.5 (STZ alone)
36	ETP 130 mg/m^2 ci, d 1–3 DDP 45 mg/m^2 ci, d 2–3, q 4 weeks	14		14	14	64	21	RD: 5 ST: 15.5
44	STZ 0.5 g/m^2, d 1–5 + DOX 50 mg/m^2, d 1+22, q 6 weeks	36	14	55	69	NR	NR	RD: 18 ST: 2.2 years
	STZ 0.5 g/m^2, d 1–5 + 5-FU 400 mg/m^2, d 1–5, q 6 weeks	33	4	42	45	NR	NR	RD: 14 ST: 1.4 years
	CHLZ[a] 150 mg/m^2, q 7 weeks	33	6	24	30	NR	NR	RD: 17
76	STZ 0.5 g/m^2, d 1–5 (ind) STZ 1 g/m^2, q 3 weeks 5-FU 400 mg/m^2, d 1–3 (ind) 5-FU 400 mg/m^2, q 3 weeks	31	0	54	54	20	25	RD: 23 ST: NR

[a]CHLZ, chlorozotocin.
NR, not recorded.

gastrointestinal side effects. The drug looks promising and deserves further evaluation. Other new drugs which have been tried in endocrine pancreatic tumors include maytansine, which has been tried by our group and by Moertel and coworkers.[6] It has generated long-lasting responses in single patients but the adverse reactions have been considerable. Another new drug which has been tried at our institution is fotemustin, a nitrosurea compound with a wide spectrum of activity, particularly in malignant melanoma. We have tried fotemustin in six patients and one patient demonstrated a significant antitumor effect lasting for more than 1 year. However, the study has now stopped because of significant toxicity, particularly very long-lasting severe thrombocytopenia.

Summary and future prospects

Chemotherapy has formed the basis for medical treatment of malignant neuroendocrine tumors for more than two decades. Streptozocin-based treatments today are the golden rule, particularly for treatment of malignant endocrine pancreatic tu-

mors. Anaplastic neuroendocrine tumors might benefit from treatment with the combination of VP-16 and cisplatin, but this has to be confirmed in larger prospective studies. In the largest group of patients (those with malignant carcinoid tumors and the carcinoid syndrome), no beneficial value of chemotherapy has so far been documented. These patients benefit more from biological treatments such as somatostatin analogs and IFNs. The role of chemoembolization has to be evaluated in forthcoming studies but it looks promising in the short perspective. Generally, standard chemotherapy has not generated significant survival times for patients with malignant carcinoid tumors, the median survival of 7–12 months should be compared with recently published data for somatostatin analogs and IFNs which give median survivals of 36 and 80 months, respectively. At our own institution the duration of remission in patients with endocrine pancreatic tumors is not significantly better for streptozocin plus 5-FU than for IFN alone. A combination of hepatic artery occlusion and systemic chemotherapy (alternating regimens) seems promising but the survival data are so far not better than for biotherapies. One explanation might be that patients with more advanced disease are included in the chemotherapy studies.

Somatostatin analogs

The observation that somatostatin inhibits the release of various peptide hormones has stimulated interest in its use as an antiproliferative agent. Somatostatin exerts a tonic inhibition of the release of several pituitary peptides including growth hormones (GH), adrenocorticotrophic hormone (ACTH), prolactin (PRL) and thyroid stimulating hormone (TSH). Somatostatin also inhibits release of several intestinal peptides such as insulin, glucagon, motilin, gastric inhibitory peptide (GIP), VIP, secretin, cholecystokinin and gastrin-releasing peptide (GRP).[47,48] The latter peptide has demonstrated growth stimulatory activity in both normal and malignant cells. GRP stimulates stimulation of normal and malignant intestinal epithelial cells, and it has been recognized as an autocrine growth factor in small cell lung carcinomas.[49] It is not yet demonstrated that somatostatin exerts an inhibitory action on traditional growth factors such as epidermal growth factor (EGF), nerve growth factor (NGF), platelet derived growth factor (PDGF) or basic fibroblast growth factor (bFGF). However, through its action via growth hormone it indirectly modulates the activity of insulin-like growth factors I and II (IGF-I and IGF-II).

Mechanisms of action of somatostatin and analogs

Somatostatin and its analogs can exert antiproliferative effects on endocrine tumors by at least two mechanisms: (i) inhibition of release of peptides from the pituitary, intestine, pancreas or (ii) direct antagonism of growth factor effects on tumor cells. Several signal transduction pathways are antagonized by somatostatin and its analogs, including effects on second messengers such cAMP, diacylglycerol (DAG), calcium channel actions and thyrosin phosphatase activation.[50–52] The precise mechanism whereby somatostatin and its analogs exert their antitumor effect is not yet elucidated. We have recently noticed that high dose (>3000 μg/day) somatostatin analog induced apoptosis (to be published).

Somatostatin receptors

Somatostatin and its analogs exert their effects through subsets of somatostatin receptors.[53] At present five subclasses of somatostatin receptors have been identified demonstrating 50–60% identity (SSTR 1–5).[54–58] All receptors belong to the seven transmembrane receptor family signalling through G-proteins. Somatostatin 14 binds to all five subclasses whereas the most common somatostatin analog octreotide (Sandostatin®) binds to somatostatin SSTR 2 and 5. The expression of various subclasses of receptors differs from different organs: SSTR 1, 2 and 3 are expressed in the pancreas, 1 and 2 in the intestine, and 1 and 5 in the lungs. SSTR 2 is highly expressed in the frontal cortex and pituitary organs, which also express SSTR 1 but at lower levels. GH secretion seems to be inhibited via SSTR2. Furthermore, inhibition of the pancreatic cancer cell line AR-4-2G, which is inhibited by octreotide, contains SSTR 2 and thus the antiproliferative effects also seem to be mediated through SSTR 2 in at least some tumor cell types. When NIH T-3 cells are transfected with SSTR 2, octreotide is able to inhibit serum and bFGF stimulated growth. It is, however, important to realize that even receptor-negative tumors can be growth inhibited by soma-

tostatin analogs, possibly indirectly via effects on other growth promoting factors such as GH or PRL and other still unknown factors.

At least three different somatostatin analogs are currently being studied in clinical trials (octreotide, Sandostatin, BIM 230146, Somatuline and RC-160, octastatin). They all bind to the same receptors, i.e. SSTR 2 and 5 (C Bruns, personal communication).

These analogs are octapeptides and the biologic action and binding to SSTRs are confined to only four amino residues within the ring structure of somatostatin, i.e. Phe-Try-Lys-Thr (amino acid residues 7–10). By incorporating D-amino acids replacing amino acids not required for biological activity, resistance to degrading is improved and has led to analogs with greatly increased and prolonged activities. Octreotide is 45–70 times more potent than native somatostatin in inhibiting GH release. The half-life in serum is increased from about 3 min for native somatostatin to more than 3 h for the analog.[59–61] Recently, long-acting formulation has been developed for all three analogs containing microcapsules for intramuscular administration. Injection of 30 mg of long-acting Sandostatin gives plasma concentrations about 1 ng/ml for almost 30 days and the drug has to be injected just once every month (C Burns, personal communication).

Somatostatin receptor scintigraphy

Somatostatin receptor scintigraphy *in vivo* has been developed recently, and is widely applied for diagnosing and localizing neuroendocrine gut and pancreatic tumors.[61–66] These tumors express somatostatin receptors SSTR 1 and 2 in almost 90% of the cases with small variations from different organs. [^{111}In]DTPA-octreotide (OctreoScan) is currently the most applied isotope and one can diagnose neuroendocrine tumors less than 1 cm in diameter, particularly when they are located outside the abdomen. SPECT can further improve the topographical localization. Receptor-negative tumors can be diagnosed in the liver as a 'black hole' as the liver takes up radiolabeled indium.[66] This method is particularly useful to identify metastases and tumors located outside the abdomen, and is of great value for 'staging' of the disease. Even if there is not a strict correlation between content of somatostatin receptors and therapeutic outcome it is of value to know whether a tumor contains somatostatin receptors when starting somatostatin therapy.

Treatment with octreotide in patients with neuroendocrine gut and pancreatic tumors

Octreotide has been registered in most countries as a drug for treatment of patients with carcinoid syndrome but also for VIP-producing tumors and the WDHA syndrome.[67]

Carcinoid syndrome

The reports from a representative sample of studies are summarized in Table 4.[67–70] Octreotide has been applied in patients with carcinoid syndrome at doses from 50 to 500 μg, three times per day. Most widely applied is 100 μg two or three times per day subcutaneously. Doses between 300 and 500 μg/day give symptomatic improvement in about 80% of the patients and a significant reduction of urinary 5-HIAA (by more than 50%) in about 70% of the patients. Doses above 500 μg three times per day have not given more subjective improvement or biochemical responses but partial tumor shrinkage has been observed in 16% of the patients. Lower doses as we have applied in earlier studies using 50 μg two or three times per day resulted in subjective responses in 50% of the patients and significant biochemical response in only 30% of the patients.[70] High dose treatment with somatuline 12 000 μg/day and octastatin 6000 μg/day has not given significantly more subjective responses or biochemical responses than intermediate dose (300–500 μg/day) treatment but a significant number of patients have demonstrated degenerative changes in biopsies from the tumors. These changes are now under investigation to look for apoptosis (to be published).

Table 4. Treatment with somatostatin analog (octreotide) in carcinoid patients

Reference	Dose	No. of patients	Biochemical response (%) (objective tumor regression)	Duration (months)
68	150 μg/d	25	72 (4)	>12
70	50 μg × 2/d	22	28 (9)	>12
69	100 μg × 3/d	14	63	

Endocrine pancreatic tumors

The only approved indication for somatostatin analogs is VIP-producing tumors and the WDHA syndrome.[67,71] The dose which has been used is median 250 μg/day (range 50–1000 μg). Eighty percent of the patients demonstrated less diarrhea with this treatment and the biochemical response has been around 70–80%. In these patients, the action of octreotide seems to be both on the tumor cell-inhibiting peptide release and also at the target cell, the secreting enterocyte. Octreotide has also been tested in gastrin-producing tumors and in the Zollinger–Ellison syndrome with a subjective improvement in about 50% of the patients and significant reduction of gastrin levels in about 33% of the patients.[67,72] The median dose in various studies has been between 200 and 600 μg/day. The effects of octreotide in patients with gastrinomas are inhibition of gastrin production from the tumor cell and also a direct effect on the parietal cell with a reduction of gastric acid output. At present H2 receptor antagonists and omeprazole are the first-line treatment for gastrin producing tumors with the Zollinger–Ellison syndrome but octroetide may be used as an adjunct in patients not responding well to these drugs. Glucagon-producing tumors are very rare, but treatment of 16 patients with doses from 200 to 300 μg/day resulted in subjective amelioration in 60% of the patients with improved skin rash in half of the patients which was not correlated to glucagon levels.[67] Octreotide seems to be effective in controlling rash and diarrhea of the glucagonoma syndrome. Insulin-producing tumors are generally small and very easy to resect with surgery. However, malignant insulin-producing tumors may be subjected to somatostatin analog treatment. The average dose of octreotide has been 200–600 μg/day and an overall improvement in hypoglycemic symptoms has been noticed in about 50% of the patients.[67] However, some caution has to be applied because some patients do very badly on somatostatin treatment because somatostatin reduces counteracting factors such as GH and glucagon relatively more than insulin, thus worsening the hypoglycemia. Therefore, insulin-producing tumors should be very carefully monitored during somatostatin treatment and hospitalized during initiation of this treatment. Other very rare neuroendocrine pancreatic tumors such as GH release factor producing tumors respond quite well to octreotide and some pancreatic polypeptide-producing tumors might also respond to the treatment.[67]

Side effects

The side effects of octreotide treatment are generally mild.[67] Fat malabsorption due to inhibitory effects of somatostatin and its analogs on pancreatic exocrine secretion is often observed. We therefore recommend pancreatic enzyme replacement when somatostatin treatment has been started. Cholestasis and subsequent cholilitiasis is also observed, and is one of the major problems during long-term somatostatin analog treatment. Sometimes cholesystectomy has to be performed to continue the treatment. During high dose treatment disturbed glucose homeostasis can be observed but it is not necessary to give the patient any antidiabetic therapy. Diabetic patients receiving octreotide treatment might have to adjust the insulin dose. A limited number of patients develop hypocalcemia due to fat malabsorption with reduced D-vitamin and calcium absorption.[70] Sometimes replacement with D-vitamins and calcium has to be instituted. Local pain is very common during octreotide treatment but can be reduced by cooling the area of injection. Injections of a drug three times per day for several years might impair the quality of life and the long acting somatostatin analogs might significantly reduce this particular problem.

In conclusion, somatostatin analog treatment in the neuroendocrine gut and pancreatic tumors is one of the most important contributions to the medical treatment of these patients. It has significantly improved their quality of life and the side effects are rather limited. Although an antitumor and antiproliferative effect has been demonstrated for cell lines and animal tumors,[73] it has not yet been demonstrated for human neoplasms *in vivo*. A lot of work still has to be done on the mechanisms of antitumor action of somatostatin analogs. In the future it seems reasonable to combine somatostatin analogs with other biotherapies such as IFNs, retinoids and possibly also luteinizing hormone releasing factor analogs.

IFN

IFN is one of the defence systems of the body. IFN production is a cellular response to substances such as microbes, tumor cells and antigens. The IFN proteins (α, β and γ) once produced induce antiviral, antimicrobal, antitumor and immunomodulatory actions. IFNs react with specific receptors on the cell surface to activate cytoplasmic signals that enter the cell nucleus to stimulate cellular genes encoding a number of proteins which carry out a

defensive action. IFN-α and -β are also called type I IFNs and exert similar effects which have mainly been explored in treatment of various tumors and hepatitis. IFN-γ is mainly an immunomodulatory agent and has recently been approved for treatment of chronic granulamatous diseases. IFN-α has been widely applied for treatment of various malignancies, particularly blood malignancies, including hairy cell leukemia, chronic melogenous leukemia and myeloma. Very few solid tumors have demonstrated any antitumor effect of IFN-α, but in patients with renal cell cancer, malignant melanoma and colorectal cancer there have been reports of some antitumor effects in 15–35% of patients given IFN-α in combination with 5-FU. Neuroendocrine gut and pancreatic tumors demonstrate differences in this from other solid tumors with IFN-α exhibiting antitumor effects in around 50% of patients. IFN-α (both human leukocyte IFN and recombinant IFN-α2b) has been registered in more than 13 countries for treatment of carcinoid tumors.[74]

IFN therapy

IFN-α was introduced by our group in the treatment of carcinoid tumors in 1982 because of its ability to stimulate natural killer cell function and to control secretion, clinical symptoms and tumor growth.[75] Since then more than 350 patients with neuroendocrine tumors have been treated with IFN-α in our institute and as many has been reported in the literature; the results are summarized in Table 5.

The largest series of patients with malignant endocrine pancreatic tumors has been treated in our institute, including 57 patients with various clinical syndromes. The median age at diagnosis was 53 years. Time from diagnosis to start of IFN-α treatment was median 33 months and the clinical syndromes included five patients with hypoglycemia, 13 patients displayed the Zollinger–Ellison syndrome, 25 cases had non-functioning tumors, 12 patients showed the Verner–Morison syndrome, with one glucagonoma and one somatostatinoma patient. In total, 43 out of these 57 patients had liver metastases at the start of treatment (75%) and 28 patients (50%) had previously received chemotherapy. The maintenance dose of natural IFN-α was 6 MU/day and of recombinant IFN-α Intron-A (IFN-α2b) 5 MU three to five times per week subcutaneously. Out of 57 patients treated with IFN-α, 29 (51%) responded with significant biochemical improvement (>50% reduction of principal tumor marker). Seven patients (12%) also showed significant tumor reduction with more than 50% reduction of tumor size displayed by computed tomography. The median duration of response was 20 months (range 2–96 months). Patients with the Verner–Morison syndrome had a higher response rate (10/12 patients) than those with other tumors. Disease stabilization occurred in 14 patients (24.5%) with a duration of 16 months (median). Patients who

Table 5. IFN-α therapy in patients with neuroendocrine tumors

Reference	No. of patients	Dose	Biochemical response (%)	Tumor response (%)
77	27	IFN- α2a 24 MU/m^2 × 3/w s.c.	39	20
83	21	IFN-α2b 3 MU/m^2 × 3/w s.c.	56	10
78	19	IFN-α2b 5 MU × VIIII/w s.c. alone* or with embolization	40*; 86	10*; 86
79	18	rIFN-α2c 2 MU/m^2 × XII/w s.c.	44	0
80	8	nIFN-α 3 MU × VII/w s.c.	50	12.5
81	37	nIFN-α 6 MU × VII/w i.m.	49	11
82	21	rIFN-α2b 5 MU × III/w s.c.	53	0
24	20	nIFN-α 6 MU × VII/w s.c.	50	11.
		versus		
		streptozotocin + 5-FU	0	0
38	111	nIFN-α × VII/w or s.c. rIFN-α2b 5 MU × III/w	42	15
85	22	rIFN-α2b 3 MU/m^2 × 3/w	25	17
		versus		
		rIFN-α2 3 MU/m^2 × 3/w + steptozotocin + adriamycin	0	0
84	11	rIFN-α2b 2.5 MU × 7/w s.c.	60	18
76	57[a]	r/nIFN-α2b 5–6 MU × III–V/w s.c.	51	12
Total	372		median: 44	median: 11

[a]Malignant endocrine pancreatic tumors.

had received prior chemotherapy (n = 28) had a biochemical response rate of 55% whereas previously untreated patients (n = 29) had a response rate of 44%. In five patients initially treated with a combination of streptozotocin plus 5-FU but displaying tumor progression, the addition of IFN-α 5 MU three times per week induced a significant biochemical response in three out of five patients; the median duration of this response was 11 months. Four patients receiving IFN-α but with progressive disease were treated with addition of somatostatin analog (octreotide) and three out of these patients showed objective biochemical responses with a median duration of 21 months. One of the patients demonstrated remarkable tumor regression, both of the primary tumor in the pancreas and of liver metastases, and could subsequently undergo curative surgery. The median survival from start of treatment in our total of 78 patients with endocrine pancreatic tumors and liver metastases undergoing subsequent treatment with chemotherapy, IFN-α or octreotide was 50 months.[76]

Carcinoid tumors

More than 300 patients with carcinoid tumors and the malignant carcinoid syndrome have been treated with IFN-α at various doses (Table 5[5,24,38,77–84]). At our institute, IFN-α was administered to 111 patients with malignant carcinoid tumors and liver metastases.[76] We obtained biochemical responses in 42% of the patients with a median duration of 32 months. Another 39% of the patients showed stabilization of their diseases without any further tumor growth. Fifteen per cent of the patients demonstrated a significant reduction of tumor size, whereas 70% experienced a subjective improvement with less flushing and/or diarrhea. Survival data on our patients with malignant carcinoid tumors where analyzed. The median survival from start of treatment was more than 80 months in the group of patients treated with IFN-α, which is 10 times longer than that of a historical group at our institute treated with chemotherapy (streptozotocin plus 5-FU), reaching a median survival of only 8 months. This historical study has of course to be evaluated in a randomized controlled study.

As indicated in Table 5, the biochemical response rates in various studies have been median 42% with a tumor response of median 11%. Moertel and colleagues[77] administered very high doses of recombinant IFN-α2a (median 48 MU every second day) which did not increase the response rate of either biochemical or tumor responses. However, they could not continue with this treatment for longer periods than a median of 8 weeks because of considerable side effects. In most other studies low to median doses have been applied with a median of about 5 MU three to five times per week subcutaneously. Obviously there is not any clear dose–response relation and the optimal tolerated dose for long-term management seems to be around 5–10 MU three to five times per week subcutaneously. Thus, it is very important to titrate the dose individually for each patient for long-term management and we have been using the leukocyte count as an indicator of antiproliferative effects of IFN-α, aiming at reducing the leukocytes below 3.0×10^9/l. Using this method, dosages for individual patients might range from 1.5 to 10 MU three to seven times per week subcutaneously. Later on, we could confirm that this empirical method correlated with the therapeutic results as well as induction of 2′–5′-A-synthetase (see below). Another important observation is obtained from a study by Hansen and co-workers[78] in which they reported increased response rates after tumor reduction by embolization of liver metastases previous to start of IFN. Therefore, reduction of tumor mass might significantly improve the therapeutic results which also might indicate that IFN-α treatment should be initiated early in the clinical course or after tumor debulking when the tumor mass is limited.

In a recent study we combined octreotide and IFN-α in patients with malignant carcinoid tumors.[37] The patients received octreotide starting with 50 μg twice a day increasing to 100 μg three times per day. If they did not respond to this dose of somatostatin analog, IFN-α was added at a median dose of 3 MU three times per week subcutaneously. Twenty-four patients were included in this study, all demonstrating increased urinary 5′-hydroxyindolacetic acid levels and 19 showed the classical carcinoid syndrome. By using this combination, patients who were previously resistant either to octreotide alone or to IFN-α alone demonstrated biochemical responses with complete biochemical remission in four out of 22 (18%) and partial remission in 13 out of 22 patients (59%). In the entire group, 77% of the patients experienced biochemical responses with a median duration of 15 months. None of these patients have demonstrated any significant tumor reduction on computed tomography. When IFN-α was withdrawn for any reason immediate increase of urinary 5-HIAA as well as clinical symptoms were noticed and when IFN-α was reintroduced a signif-

icant amelioration of symptoms and reduction of U-5HIAA was noticed.

In a randomized controlled trial including 22 patients we have combined recombinant IFN-α2a 3 MU/m^2 three times per week with streptozotocin 1 g/m^2 plus doxorubicin 40 mg/m^2 versus IFN alone in the same dose.[85] The chemotherapy was administered every 3 weeks. In total, 22 patients with malignant carcinoid tumors and the carcinoid syndrome were enrolled, 11 in each arm. We could not see any beneficial value of adding the chemotherapy to IFN-α. On the contrary, both biochemical (25%) and tumor responses (17%) were less than expected for IFN alone. Moreover, considerable side effects were encountered; one patient died from doxorubicin-related cardiotoxicity thus IFN-α might have increased the cardiac sensitivity for doxorubicin.

In a phase I–II study including 12 patients with malignant carcinoid tumors a combination of IFN-α and human IFN-γ (Finnish Red Cross, Helsinki) was used.[86] All patients were treated with IFN-α at a dose of 5–10 MU three to five times per week for a median of 22 months and showed stable or progressive disease. IFN-γ was then added at a daily dose of 0.5 MU subcutaneously. After 6 months treatment there was one partial response, seven patients showed stable disease and three patients had progressive disease. One patient was withdrawn from the study. Half of the patients experienced subjective improvement but no significant tumor reduction was noticed.

Adverse reactions

The adverse reactions of IFN-α therapy are listed in Table 6. They include 'flu-like' symptoms for the initial 3–5 days in almost all patients but these adverse events could easily be prevented by concomitant administration of paracetamol. More severe adverse reactions are fatigue (grade I–II) in about 50% of the patients, low grade weight loss in 59% of the patients and sometimes mental depression. About one-third of the patients may develop increased expression of liver enzymes which are mainly dose dependent and about 20% of the patients develop autoimmune reactions. Patients treated with recombinant IFN-α may develop neutralizing IFN antibodies in various degrees to different IFN preparations which might abrogate the antitumor response (Table 7). In such patients a change from recombinant IFN to human leukocyte IFN might restore the antitumor effect.

Table 6. Adverse reactions in 111 patients treated with IFN-α

	%	WHO grade
'Flu-ike' symptoms	89	1–2
Weight loss	59	1
Fatigue	51	1–2
Anemia (<110 g/l)	31	1
Leukopenia (<2.0×10^9/l)	7	1
Thrombocytopenia (<100×10^9/l)	18	1
Hepatotoxicity	31	1–2
Increased blood lipids	32	1–2
Autoimmune manifestations	20	
Neutralizing IFN antibodies	1–38	

Mechanism of antitumor action of IFN-α

The antitumor effects of IFN-α include antiproliferation, apoptosis, differentiation and cytotoxic/cytostatic effects. Furthermore, IFN-α clearly demonstrates an immunomodulatory effect by increased expression of class I antigens on tumor cells and induction of autoimmunity.[76,87] IFN-α or type 1 IFNs bind to a specific cell membrane receptor which is not yet fully cloned. Binding of IFN to its receptor phosphorylates tyrosine kinases called TYK-2, JAK-1 and JAK-2 which then activate IFN-sensitive growth factor 3 (ISGF-3) by phosphorylation. This complex is transported into the cell nucleus and binds to IFN-sensitive response elements (ISREs) which starts transcription of several IFN inducible genes (ISGs). There are at least more than 30 ISGs, some of which act as tumor supressor genes (IRF-1) whereas others might act as oncogenes (IRF-2). The antiproliferative effect of IFN-α is mediated through induction of enzymes such as 2′–5′-A-synthetase and p-68 kinases (PKR). Both enzymes induce a degradation of mRNA for various

Table 7. Development of neutralizing IFN-α antibodies in patients with neuroendocrine tumors

	No. of patients treated	No. of positive patients	%	No. of patient with titres >400 NU
HuLe-α	103	(1)[a]	(1)	(1)(1%)
Wellferon	16	(1)[a]	(6)	—
IFN-α2b	208	21	10	7 (3%)
IFN-α2a	32	12	38	11 (34%)
Total	359	35	10	19 (5%)

[a]Partial neutralization after previous IFN-α2a treatment.
[b]Partial neutralization after previous IFN-α2b treatment.

peptide hormones and growth factors which result in inhibition of protein synthesis.[88,89] We have demonstrated that the induction of 2′–5′-A-synthetase *in vitro* in tumor cells is correlated with the clinical and biochemical responses.[89] Patients who demonstrate more than a 3-fold increase of basal 2′–5′-A-synthetase levels after adminstration of IFN-α clearly respond biochemically, whereas those with low induction were non-responders. Recently we looked upon activation of another IFN-inducible protein called Mx-A protein but we could not find any correlation between antitumor effect and induction of Mx-A mRNA in peripheral leukocytes from patients with neuroendocrine tumors (to be published). Another effect of IFN-α is induction of fibrosis within liver metastases which has not been recorded during treatment with chemotherapy or somatostatin analogs. With time the number of tumor cells decreases and they are replaced by fibroblasts without any change in tumor size recognized by ultrasound or computed tomography scans.[90] However, such changes in tumor composition can be clearly detected both by positron emission tomography (PET) where accumulation of ^{11}C-labeled hydroxytryptophan or L-dopa correlate with the metabolism of the tumor. Also, somatostatin receptor scintigraphy can demonstrate changes in tumor content. The antiproliferative effect of IFN-α is mainly due to blocking of the cell cycle in the G_0/G_1 phase with very low numbers of S phase cells after IFN-α administration. Rather early during treatment with IFN-α a reduction in hormone release and synthesis can be noticed (within days to months), whereas significant tumor reduction takes a longer time (up to years). It is important to realize that IFN-α does not act in a similar way as chemotherapy, and there is no clear correlation between dose and antitumor response. It is therefore important to titrate the dose for each patient individually for long-term treatment. We have at present patients who have been treated continuously for more than 10 years with IFN-α with continuing biochemical and tumor responses.

To summarize, IFN-α has demonstrated a significant antitumor effect in neuroendocrine gut and pancreatic tumors. Combination of IFN-α with another biological response modifier, i.e. octreotide, seems very promising. Future studies will show the precise role of this combination treatment. Adverse reactions of IFN-α are mostly dose dependent and it is important to individualize the treatment for each patient. Today predictive testing can be performed using induction of 2′–5′-A-synthetase. PET might be the future tool to follow patients on IFN treatment. The treatment with IFN-α seems to be life-long and it is important to realize that the therapy is not curative but can control the disease for extended periods of time. Survival seems to be significantly prolonged during IFN-α treatment and it is accompanied by a fairly good quality of life.

Pure symptomatic treatment

Patients with neuroendocrine tumors of the gut and pancreas present various clinical symptoms, the most common including diarrhea, flushing, acid hypersecretion, and hypo- and hyperglycemia. By introduction of somatostatin analogs most of these symptoms can be controled by just one drug and a lot of older therapies have been omitted today. Somatostatin analogs control flushing and diarrheas in many patients, and sometimes also acid hypersecretion, hypoglycemia as well as hyperglycemia. Still, there is a need for other drugs to be used in adjunct with chemotherapy, IFNs or somatostatin analogs. Among these are the most important H_2 receptor blockers in patients with acid hypersecretion and more recently omeprazole, which is even more effective in controlling acid hypersecretion and preventing gastric and duodenal ulcers.[91] The dosage of both these types of drugs is aimed at establishing a low basal acid output (below 10 mmol/h). H_2 receptor blockers present more side effects than omeprazole but the latter is more expensive. The long-term safety of omeprazole is still debated but we have been treating Zollinger–Ellison patients for 11 years continuously on 20–60 mg/day without seeing any particular side effects or increased incidence of gastrointestinal malignancies. Older patients with hypoglycemic symptoms due to insulin-producing tumors which cannot be operated or younger patients where the tumor is not localized can be treated with diazoxid in doses of 150–800 mg/day.[92] The efficacy of diazoxid is increased and the tendency for edema is reduced when it is administered along with diuretics. Diazoxid primarily inhibits granular insular secretion in response to glucose but it is not effective in all patients because many insulin producing tumors lack insulin granules. The main side effects of diazoxid are gastrointestinal irritation, nausea, hypertension, edema and hirsutism. Diarrheas in patients with carcinoid tumors and VIP-producing tumors can in many situations be controled by somatostatin analogs. Sometimes the analog by itself induces steatorrhea and diarrhea even when pancreatic enzymes are substituted. Therefore, in pa-

tients with the carcinoid syndrome and diarrhea the addition of the morphine analog loperamide is beneficial and is able to control diarrheas in many patients. Previous treatment with cyproheptadin (Periactin®) and metysergid (Sansert®) is no longer indicated after the introduction of somatostatin analogs. In patients with foregut carcinoids with histamine production, cyproheptadin might still play a role in controlling flushes. Some patients with mechanical courses of diarrhea after surgery or by the tumor itself might benefit from addition of cholestyramine (Questran powder), adjusting the doses according to the diarrhea and the patient's tolerance. Many patients with midgut carcinoids have had resections of the terminal ileum and therefore should receive B12 supplementation.

Conclusion

During the last decade a more active approach to patients with neuroendocrine tumors has evolved. The surgery has been more aggressive with wide resections to reduce the tumor bulk as much as possible, and with the introduction of biotherapies, somatostatin analogs and IFNs, further improvements in the quality of life and survival has emerged. Still, today, very few patients with malignant disease and metastatic spread are actually cured by the available treatment. To further improve the treatment and enable more complete cures among our patients, we have started a prospective program to define the tumor biology in each individual and after that to 'tailor make' the optimal treatment. This tumor biology program includes studies of proliferation capacity with Ki-67, expression of growth factors and growth factor receptors, PDGF, bFGF, transforming growth factor-β and particularly PDGF-α receptor, which seems to be correlated to bad prognosis, at least in some tumor types.[93] Furthermore, expression of adhesion molecules such as cadherines and CD44 will further enhance our understanding of the tumor biology. Future treatment might also include gene therapy since we have recently identified a tumor suppressor gene for multiple endocrine neoplasia type 1 (MEN 1) and the expression of this gene seems to be also impaired in sporadic neuroendocrine tumors (to be published). Since growth regulatory signals in neuroendocrine tumor cells seem to be mediated both through tyrosine kinase receptors and G-protein coupled receptors, drugs affecting both these pathways might be of importance for forthcoming successful treatment.

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