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MEDICAL TREATMENT OF NEUROENDOCRINE GUT AND PANCREATIC TUMORS

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Abstract

Surgery has always been considered to be the primary treatment in patients with neuroendocrine gut and pancreatic tumors, but a significant number of patients present liver metastases already at the first visit. There is obviously a need for effective medical treatment and in the present paper we report our experience of treatment with chemotherapy, the somatostatin analogue SMS 201-995 and interferons. In 30 patients with malignant endocrine pancreatic tumors, chemotherapy including streptozotocin plus 5-fluorouracil had an objective response rate of 63% with a mean duration of the objective response of 17.4 months. There was a difference between clinically functioning and nonfunctioning tumors, which had objective response rates of 68% and 50% and mean response duration of 21 and 9.4 months respectively. The new somatostatin analogue SMS 201-995 was used in 10 patients giving an objective response rate of 40% with a mean duration of 13.5 months. In a series of 22 patients treated with human leukocyte interferon, an objective response rate of 77% was obtained with a mean duration of 8.5 months. A combination of streptozotocin plus 5-fluorouracil gave an objective response rate of 10% with a mean duration of 2.7 months among 31 patients with midgut carcinoid tumors. The somatostatin analogue SMS 201-995, tested in 22 patients with carcinoid tumors, gave an objective response rate of 28% with a mean duration of 18.5 months. Interferon has been tried in three separate studies. The first study, including 36 patients with malignant carcinoid tumors treated with human leukocyte interferon, showed an objective response rate of 47% with a mean duration of 34 months. In a randomized controlled study, where human leukocyte interferon was compared with streptozotocin plus 5-fluorouracil including 10 patients in each arm, no objective response was obtained during the six months' observation in the group of patients receiving chemotherapy, whereas 50% responded in the interferon-treated group. In the third study, IFN-α_{2b} or IntronA was tested in 20 patients with malignant carcinoid tumors and gave an objective response rate of 55% during a six-month observation period. With regard to these data chemotherapy and interferons seem to be equally potent in the treatment of malignant endocrine pancreatic tumors, whereas interferons seem to be superior to both chemotherapy and the somatostatin analogue SMS 201-995 in malignant carcinoid tumors. The somatostatin analogue has proved to be particularly useful in the treatment of patients with severe hormone-related clinical symptoms and in the perioperative period. The analogue can be combined with interferon or chemotherapy for controlling severe clinical symptoms.

Key words: Neuroendocrine tumors, gut, pancreas, chemotherapy, interferons, somatostatin analogues.

Neuroendocrine tumors of the gut and pancreas constitute about 2% of all malignant tumors of the gastrointestinal tract. The 2 main groups of endocrine tumors in this region are the carcinoids and endocrine pancreatic tumors. The annual incidence of malignant carcinoid tumors found at autopsy was 2.1/100 000 population (1) but from our own data we found an annual incidence of clinically significant tumors of 0.7/100 000 population (2). The annual incidence of endocrine pancreatic tumors was found to be 0.4/100 000 population (3). A more frequent recognition of endocrine tumors of the gut and pancreas within the past decade can be largely attributed to the better characterization of associated clinical syndromes coupled with improved diagnostic methods. The most important factors, facilitating the clinical recognition of new syndromes, have been the development of radioimmunoassays for an increasing number of circulating polypeptide, and immunocytochemistry for examining tissue sections.

Malignant carcinoid tumors present rather uniform clinical symptoms and are slowly advancing, whereas neuroendocrine tumors of the pancreas have more varied progression rates and symptomatology. Treatment should have the dual aims of controlling tumor growth and clinical symptoms. During the last few years a more aggressive surgical and medical treatment policy has emerged.

Surgery should always be considered in patients with endocrine tumors of the gut and pancreas. Even if total excision of the tumor cannot be achieved, debulking pro-

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cedures with a reduction of tumor mass may improve the patients' symptoms and also facilitate forthcoming medical treatment.

Hepatic artery ligation or embolization of the hepatic arteries to reduce the number and size of liver metastases may bring about useful palliation and can be used at any time during the course of treatment. Contradicting data on irradiation have been reported and at present irradiation is only used for palliation of bone metastases.

The following chapter will concentrate on causative medical treatment of patients with malignant endocrine pancreatic tumors and carcinoids. Three different therapeutic regimens will be discussed; namely chemotherapy, somatostatin analogues and interferons. The data presented are based on our own experience from all these types of therapy and compared with reports from the literature.

Table 1

Medical treatment of malignant endocrine pancreatic tumors

Chemotherapy	n	OR%	SD%	PD%	Mean duration of response (months)
Streptozotocin + 5-FU	30	63	19	18	17.4
'Functioning' tumors	22	68	20	12	21
'Nonfunctioning' tumors	8	50	10	40	9.4
SMS 201-995	10	40	30	30	13.5
Interferon (Hu-Le IFN-α)	22	77	5	18	8.5

OR = objective response.
SD = stable disease.
PD = progressive disease.

Chemotherapy

Endocrine pancreatic tumors. In 1968, Murray-Lyon et al. (4) reported a single patient with advanced islet cell carcinoma who had a dramatic response to streptozotocin, an antibiotic which produces specific islet cell toxicity in animal models. Five years later, in a series of 52 patients collected by Broder & Carter (5) through the National Cancer Institute, 54% of the patients had reduction of biochemical manifestations of the tumors and 37% had at least partial tumor response to streptozotocin. In a large randomized trial by the Eastern Cooperative Oncology Group (ECOG) (6) comparing streptozotocin alone with streptozotocin plus 5-fluorouracil, the combination regimen produced both a greater overall rate of response (63% versus 36%) and a greater rate of complete remissions (33% versus 12%). The median survival with the combination was also greater (26 months versus 16.5 months) but the differences did not reach statistical significance.

The response rate was somewhat higher in patients with functional tumors than in those with nonfunctional ones (80% versus 62%), but this difference was not statistically significant.

In our own series of 30 patients with malignant endocrine pancreatic tumors (7), an objective response rate of 63% was obtained with a mean duration of 17.4±13 months (Table 1). The currently used dose schedules for streptozotocin have been 0.5 to 1.0 g/m^2 daily for 5 days repeated every 6 weeks or given as bolus dose of 1 g/m^2 every third week after initial induction of 0.5 to 1.0 g/m^2 for 5 days. When combined with 5-fluorouracil or doxorubicin, the doses of these 2 drugs are 400 mg/m^2 and 40 mg/m^2 respectively. The most severe adverse reactions of streptozotocin are severe vomiting and renal failure.

Other cytotoxic agents have been used in a limited number of patients, both as single therapy and in combinations. Doxorubicin alone gave an objective response in 19% of patients, whereas chlorozotocin, DTIC, melphalan, and maytansine have been used only in small groups of patients (8). Dacarbazin (DTIC) has been reported to give favorable response in patients with glucagonomas (9).

Carcinoid tumors. A variety of chemotherapeutic drugs have been used in the treatment of patients with malignant carcinoid tumors. 5-fluorouracil used at a dose of 500 mg/m^2/day in 5-day courses, repeated every 5 weeks, gave an objective response rate of 18% (ECOG) (10).

Doxorubicin administrated at a dose of 60 mg/m^2 every third to fourth week gave in one report objective response in 21% (ECOG) (10).

Dacarbazin used in a Mayo Clinic trial gave an objective response rate of 17% among 18 patients (11).

Cisplatinum administrated at doses of 45–90 mg/m^2 by intravenous infusion have reported to give objective responses in only 7% (12).

Streptozotocin used as single agent has been reported to give objective response in 1 out of 6 patients in one report (15) and in none out of 8 patients in another (13).

Combination therapy has been used in patients with malignant carcinoid tumors, mainly combinations of streptozotocin and 5-fluorouracil, cyclophosphamide or doxorubicin. In a randomized multiinstitutional trial performed by ECOG, the combination of 5-fluorouracil plus streptozotocin was compared with streptozotocin plus cyclophosphamide. The objective response rates were 33% and 26% respectively. The trial comprised more than 80 patients in the 2 arms. The response rates were significantly greater for small bowel carcinoids than for carcinoids of pulmonary or unknown origin (14).

In our own material of 31 patients with malignant carcinoid tumors, treated with streptozotocin in a combination with 5-fluorouracil, we could only obtain objective responses in 10% of the patients with a short remission time of 2.7 months (Table 2) (15).

In a small series of 10 patients with malignant carcinoid

Table 2

Medical treatment of malignant carcinoid tumors

Chemotherapy	n	OR%	SD%	PD%	Mean duration of response (months)
Streptozotocin + 5-FU	31	10	57	33	2.7
SMS 201-995	22	28	36	36	18.5
Interferon					
Hu-Le IFN-α	36	47	39	14	34
Hu-Le IFN-α vs Streptozotocin + 5 FU	10	50	50	0	6*
	10	0	50	50	-
IFN-α_{2b} (Introna)	20	55	30	15	6*

OR = objective response.
SD = stable disease.
PD = progressive disease.
* = the study only lasted for 6 months.

tumors, a combination of streptozotocin plus doxorubicin gave an objective response in 4 patients (40%) (16). A 4-drug regimen of 5-fluorouracil, streptozotocin, doxorubicin and cyclophosphamide does not appear to have offered any clear therapeutic advantages with 7 of 20 (35%) patients showing response (17).

In summary, streptozotocin in combination with 5-fluorouracil or doxorubicin has so far demonstrated significant antitumor effects in patients with malignant endocrine pancreatic tumors. However, in other neuroendocrine tumors, the objective response rates are low, ranging about 10–30%. The adverse reactions of the chemotherapy regimens are significant and the treatment is not curative.

Somatostatin analogues

Naturally occurring somatostatin is a well-known inhibitor of hormone release and has been used for treatment of clinical symptoms in patients with malignant neuroendocrine gut and pancreatic tumors. The disadvantage with this treatment is a short plasma half-life of natural somatostatin. During recent years, somatostatin analogues have been developed of which the most widely investigated one is SMS 201-995 (Sandostatin); a synthetic octapeptic analogue of somatostatin. Compared to natural somatostatin this analogue has an extended plasma half-life (~100 min) with clinical effects up to 4 h after subcutaneous injection and can be administered 2 or 3 times per day by the subcutaneous route (18).

Endocrine pancreatic tumors. Several studies have been performed with this compound in patients with neuroendocrine pancreatic tumors at varied doses, ranging from 50 μg twice daily to 150 μg three times per day. The results from a multiinstitutional study of 48 patients gave the following objective response rates: 7 of 13 patients with VIPoma had a significant reduction of hormone levels, 2 of 6 patients with glucagonoma achieved an objective response as did 7 of 14 patients with gastrinomas and both patients with GRFomas (personal communication). None of 12 patients with insulinomas had significant reduction of insulin and clinical symptoms deteriorated. Subjective improvement was more common than objective responses and the compound proved to be particularly useful in patients with the WDHA syndrome.

In our study of 10 patients with a variety of malignant endocrine pancreatic tumors, 4 patients achieved more than 50% reduction of peptide levels with a median duration of 13.5 months (Table 1) (19). All 4 patients improved symptomatically and had less dyspeptic symptoms and decreased diarrhea. In addition, a further 3 patients had total relief of symptoms without any effect on tumor secreted peptides. The other 3 patients progressed on treatment. No objective reduction of tumor mass was noted in any of the patients. We found the somatostatin analogue treatment to be well tolerated, but a minority of patients developed steatorrhea and hyperglycemia.

Carcinoid tumors. Our initial experience with long-acting somatostatin analogue SMS 201-995 was very favorable in terms of ameliorating symptoms related to the carcinoid syndrome (20). The subjective improvement was noticed initially in all 5 patients treated, but the disease progressed in 2 cases. We have now extended the material and in a recently closed study, including 23 patients with malignant midgut carcinoids, 6 out of 22 evaluable patients (28%) showed objective tumor response lasting for 6 to 30 months. Stable disease was obtained in 8 of the 22 patients (36%) and progressive disease in a further 8 patients (36%) (Table 2) (to be published). Subjective response with decrease of diarrhea or flushing was noticed in 11 out of 22 patients (50%). Two out of 6 patients with objective response also demonstrated a significant decrease of tumor size lasting for 6 and 30 months respectively. The patients received 50 μg twice daily of SMS 201-995 for 6 months, and thereafter the dose was increased to a median of 100 μg twice daily. In order to maintain the clinical response, the dose had to be increased in all 6 responders. The adverse effects included development of diabetic blood glucose levels in 8 out of 22 patients (36%). Albumin modified serum calcium levels was significantly decreased after receiving SMS 201-995 and one patient developed symptoms of hypocalcemia which was reversed by supplementation with calcium and D-vitamins.

In a similar study by Kvols et al. (21), 21 patients with histologically proven metastatic carcinoid tumors and carcinoid syndrome were treated with subcutaneous injections of Sandostatin (SMS 201–995) at doses of 150 μg 3 times daily. Flushing and diarrhea associated with the syndrome were promptly relieved. Fifteen of the 21 patients (71%) had a more than 50% reduction of 5-hy-

droxy-indole-acetic levels (u-5-HIAA) and the median duration of the biochemical response was more than 9 months. No objective shrinkage of the tumors was noticed (see the article by Kvols (p. 433 in this issue)). In summary, the somatostatin analogue SMS 201-995 has demonstrated significant effects on hormone-related clinical symptoms in patients with malignant neuroendocrine gut and pancreatic tumors. The objective response rates in patients with malignant carcinoid tumors range between 28% and 71%. The drug has been particularly useful in patients with severe flushing and diarrhea and has also been beneficial for the pre-, post-, and intraoperative management of carcinoid patients. Pretreatment with the somatostatin analogue can almost completely abolish the release of tachykinins in patients with carcinoid syndromes and concomitantly reduce the flushing attack (Figure). Whether the analogue might exert any cytotoxic effect is not yet proven, but in a limited number of patients, tumor shrinkage has been observed for shorter periods of time. Such a reduction of tumor size might be induced by inhibition and reduction of tumor secreted growth factors and blocking autocrine loops of stimulation of carcinoid tumor growth. During long-term treatment, the tendency of decreased 'sensitivity' to the somatostatin analogue has been observed. This might be due to a down regulation of the somatostatin receptors. Among patients with malignant endocrine pancreatic tumors, those with WDHA syndrome showed the most beneficial effect of the analogue. Treatment of insulinomas seem to be more dubious because of observed worsening of the hypoglycemia during therapy, probably due to more pronounced effects on counter regulatory peptides, such as glucagon and growth hormone.

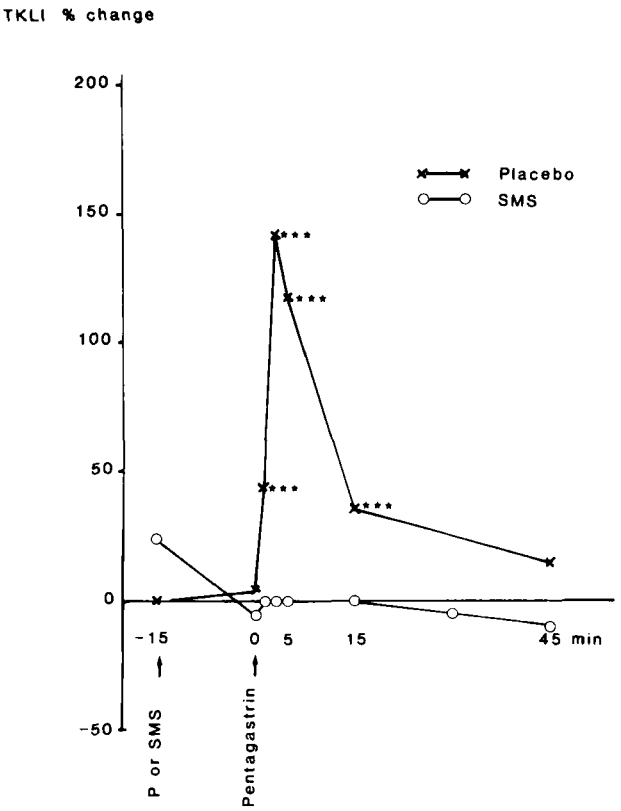

Figure. The release of plasma tachykinins in patients with carcinoid tumors during flush provocation with pentagastrin before (*—*) and after (○—○) pretreatment with somatostatin analogue SMS 201-995. ***=p<0.001.

Interferons

Interferons is a group of proteins induced by viral infection with demonstrated antitumor effects in a number of hematologic malignancies (see articles by Strander (p. 355) and Gresser (p. 347) in this issue). Most commonly used are alpha interferons, both naturally occurring and recombinant forms. In the patients treated with interferons, the antitumor effects may be achieved by effects on oncogenes and growth factors and through direct cytostatic effects. It is equally possible that the antiviral, differentiation and receptor effects are more important.

Our first trial with human leukocyte interferon in patients with malignant carcinoid tumors started in 1982 (22). We could demonstrate a significant reduction of hormone production, but no effect on tumor size after 3 months' therapy. The number of patients in different studies with the natural leukocyte interferon and recombinant alpha interferons is now well above 100.

Endocrine pancreatic tumors. We started to use human leukocyte interferon in 1983 in 2 patients with malignant endocrine pancreatic tumors and the WDHA syndrome. Both patients had earlier been treated with chemotherapy

Table 3

Adverse effects of interferon in long-term study of carcinoids

Adverse effect	Incidence (% of patients)
'Flu-like' symptoms	89
Decreased hemoglobin content	58
Anemia (<110 g/l)	31
Decreased No. of leukocytes	67
Leukocytes ($<2.0\times10^9$/l)	3
Decreased No. of platelets	74
Platelets ($<150\times10^9$/l)	14
Increased liver enzymes	
s-ASAT	31
s-ALAT	31
s-Alkaline phosphatases	22
s-Bilirubin	8
s-LD	6
Increased blood lipids (s-Triglycerides)	32
Liver steatosis	19
Thyroid autoantibodies	15
Hypothyroidism	6
Parietal cell antibodies	3
SLE-syndrome	3
Leukoplasia (buccal)	3
Mental depression	3

but showed tumor progression with severe diarrheas up to 10 l/day. A significant reduction of the diarrheas occurred within one week and was followed by concomitant decrease of the plasma VIP levels (23). We were able to control the disease for 3 years in one of the patients with a dose of human leukocyte interferon of 3–6 MU/day subcutaneously. In a recent study, we demonstrated an objective response in 17 out of 22 patients with malignant endocrine pancreatic tumors during treatment with human leukocyte interferon 3–6 MU/day (Table 1). All patients had tumor progression prior to interferon therapy and had been subjected to chemotherapy including streptozotocin plus 5-fluorouracil or doxorubicin with failing effect.

A more than 50% reduction of tumor markers and/or tumor size was observed in all 7 patients with WDHA syndrome, in 3 out of 4 with Zollinger-Ellison syndrome, in 6 out of 9 with nonfunctioning tumors, and in 1 patient with somatostatinoma. The median duration of response was 9.5 months (range 2–36 months). In 6 of the 17 responders, a more than 50% decrease in tumor mass was noted and 2 patients had a complete remission. In 15 of the responders decreasing tumor marker levels were observed. The number of patients with malignant endocrine pancreatic tumors treated with human leukocyte interferon has now been extended to 27 and an objective response has been obtained in 22 (73%). Both patients with hormonally active tumors and so-called 'nonfunctioning' tumors, have shown objective responses to interferon treatment.

The adverse reactions of interferon treatment are considerably less than with chemotherapy, and include short lasting flu-like symptoms, weight loss, mild anemia and leukopenia (Table 3).

Carcinoids (Table 2). We have performed 3 different studies of interferons in the treatment of malignant carcinoid tumors. In our long-term study, 36 patients with carcinoid tumors (29 patients with midgut carcinoids, 4 lung carcinoids, 1 with rectal carcinoid, 1 ovarian and 1 unlocalized primary tumor) were included. Thirty-two out of 36 patients had liver metastases and 19 of 36 patients had received previous cytotoxic treatment with progressive tumor disease. Human leukocyte interferon at doses of 3–6 MU/day subcutaneously were used. An objective tumor response was achieved in 17 of the 36 patients (47%), 14 of 29 patients with midgut carcinoid (48%) and 3 of the 4 patients with lung carcinoids (75%). The disease remained stable in 14 patients (39%) and progressed in only 5 (14%). Sixteen of the 17 patients with objective responses had significant decrease of tumor markers and in 4 of them also a significant reduction of tumor size. Two patients showed complete remission. The median duration of objective response was 34 months and the median duration of stable disease was 25 months.

In a second study, which was randomized and compared leukocyte interferon with streptozotocin plus 5-fluorouracil in malignant midgut carcinoid tumors, 20 patients were included. The doses of streptozotocin and 5-fluorouracil were those recommended by other investigators and the patients received 6 MU of human leukocyte interferon 5 times per week subcutaneously (s.c.). Ten patients were included in each arm. After 6 months of therapy an objective response was noticed in 5 of 10 patients with interferon (50%), but none of the patients on chemotherapy responded. Stable disease was observed in 50% of the patients on interferon and in 50% of the patients on chemotherapy. The disease progressed in 5 of the patients (50%) on chemotherapy but in none of the patients on interferon. A χ^2-analysis of the proportions of patients with therapeutic responses showed that interferon was significantly better than chemotherapy ($p=0.0067$).

In the third study, 20 patients with malignant carcinoid tumors were treated during 6 months with recombinant interferon-α_{2b} (Introna) at a mean dose of 5.9 MU 3 times per week s.c. Eleven of the patients had earlier received natural leukocyte interferon which was withdrawn 3–12 months prior to treatment with recombinant interferon-α_{2b}. Nine patients were previously untreated. Eleven of the 20 patients (55%) demonstrated a more than 50% reduction of tumor markers. Six patients (30%) remained stable, whereas 3 (15%) showed progressive disease. These results are quite similar to those reported earlier for treatment with natural leukocyte interferon in patients with malignant carcinoid tumors. There was no difference in tumor response between the patients who previously had received natural leukocyte interferon and those who were untreated, which implies that interferon treatment can be withdrawn for extensive periods of time (up to 12 months) and then reinstituted with similar good clinical response. Only 2 patients demonstrated a slight reduction of tumor size after 6 months' treatment.

The adverse events in patients treated with interferon and malignant carcinoid tumors were quite similar to those reported for other types of tumors including endocrine pancreatic tumors (Table 3). However, about 20% of the patients developed autoimmune phenomena, which has not been published earlier. There was no difference between human leukocyte interferon and recombinant IFN-α_{2b}. Nevertheless 3 patients (15%) developed neutralizing antiinterferon antibodies to recombinant IFN-α_{2b}. Two of these patients showed initially an objective response but the disease again progressed after development of interferon antibodies. In one of these patients, reinstitution of natural leukocyte interferon gave objective tumor response.

Our results of interferon treatment in patients with carcinoid tumors have been confirmed by Smith et al. (26), Doberauer et al. (27), Hansen et al. (28) and Moertel (29), who have reported objective response rates of about 40–60% and even higher after previous embolization followed by interferon treatment (80%) (28).

In summary, alpha interferons have demonstrated sig-

nificant antitumor effects in patients with both endocrine pancreatic tumors and carcinoids. The objective response has mainly concerned the tumor markers, whereas the tumor has remained unchanged for extended periods of time. The longest treatment period so far is more than 5 years in a limited number of patients. We have been able to demonstrate that although the tumor remains unchanged in size on CT-scan or ultrasound, the content of tumor cells diminishes continuously during interferon treatment with a concomitant increase of connective tissue (Cancer Research, in press). Such a mechanism of action has not been demonstrated for chemotherapy or the somatostatin analogue. This observation might indicate that interferon acts as a cytotoxic drug directly on the tumor cells or inhibits the cell division by prolongation of cell cycle phases, whereby a net tumor cell loss is achieved. Interferons might also stimulate the development of mesenchymal cells and the fibrotic process. We have also been able to demonstrate that intraarterial infusion of recombinant IFN-α_{2b} directly into the tumor causes an immediate release of stored peptide (NPK) within 15–30 min, indicating a direct action of alpha-interferon on tumor cells. Furthermore, alpha-interferons stimulate increased expression of class I antigens on the cell surface of carcinoid tumor cells (30). There is increasing evidence that stimulation of 2-5-A synthetase in tumor cells by interferon correlates well with the effect of interferon treatment in vivo. We have observed that interferon can stimulate carcinoid tumor cells to induce 2-5-A synthetase.

General discussion

Currently available chemotherapy still plays a role in the endocrine pancreatic tumors, but should not be used in patients with malignant carcinoid tumors. The objective response rates in the last group are very low and the side effects severe with reduction of quality of life. There is so far no observation that chemotherapy might prolong survival in patients with malignant carcinoid tumors and the carcinoid syndrome. During recent years, with introduction of somatostatin analogues and interferons, a significantly more effective medical treatment has become available. In our hands, interferons seem to be more suitable for long-term treatment than SMS 201-995. The doses of interferons should be low, in the range of 3–6 MU 3 to 5 times per week. The patients do no benefit from higher doses but the adverse reactions with fatigue and weight loss will increase. The 5-year survival from diagnosis for patients with malignant midgut carcinoid tumors and liver metastases in our material is now 70%, to compare with 23% in the previous report by Moertel et al. on the natural history of this disease (31). The 5-year survival for different chemotherapeutic regimens are in the range of about 20–38% (32). The optimal way of administrating interferons, alone or in combination with chemotherapy or with other immune response modifiers, needs to be evaluated by further studies. A combination with the somatostatin analogue might also be of value.

The somatostatin analogue SMS 201-995 is a very potent inhibitor of clinical symptoms and might also reduce circulating hormone levels and in rare cases cause a reduction of tumor size. Because of development of tachyphylaxis, the drug is more useful for short-term treatment and in patients with very severe clinical symptoms. The drug has to be administered at least 2 or 3 times per day at doses of 200–600 μg/day. The analogue is particularly useful in acute situations perioperatively or in carcinoid crises of other causes.

The optimal treatment for neuroendocrine tumors is not yet known. Future multicenter studies including both interferons and somatostatin analogues should be performed to elucidate the precise role of both agents in the treatment. In our opinion both agents are active in the treatment of neuroendocrine tumors and one can select between both drugs depending on the type of patients and their clinical status. It is also useful to have several agents available since decreased 'sensitivity' for one drug might develop very often during long-term treatment.

We recommend at present alpha-interferons as a basic medical treatment and that the somatostatin analogue could be used as an adjunct initially during treatment or in special patients with old age, severe weight loss, or autoimmune diseases. The somatostatin analogue should also be used in perioperative situation.

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