Prospective, Randomized, Multicenter Trial on the Antiproliferative Effect of Lanreotide, Interferon Alfa, and Their Combination for Therapy of Metastatic Neuroendocrine Gastroenteropancreatic Tumors—The International Lanreotide and Interferon Alfa Study Group

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Purpose: **Somatostatin analogs and interferon alfa control hormone-active/functional neuroendocrine gastroenteropancreatic tumors. In addition to hormonal control, variable degrees of antiproliferative effects for both agents have been reported. Until now, however, no prospective, randomized studies in therapy-naive patients have compared somatostatin analogs or interferon alfa alone with a combination of the two.**

Methods: **Eighty therapy-naive patients with histologically verified neuroendocrine tumor disease (primary localization: foregut, n = 36; midgut, n = 30; hindgut, n = 3; unknown, n = 11; functional, n = 29; nonfunctional, n = 51) were randomly treated either with lanreotide (1 mg three times a day administered subcutaneously [SC]) or interferon alfa (5×10^6 U three times a week SC) or both. All patients had disease progression in the 3 months before study entry, verified with imaging procedures.**

Results: **Twenty-five patients were treated with lanreotide, 27 patients were treated with interferon alfa, and 28 patients were treated with the combination. Partial tumor remission was seen in four patients (one patient who received lanreotide, one patient who received interferon alfa, and two patients who received the combination). During the 12 months of therapy, stable disease was observed in 19 patients (seven patients who received lanreotide, seven patients who received interferon alfa, and five patients who received the combination), whereas tumor progression occurred in 14 of 25 patients (lanreotide), 15 of 27 patients (interferon alfa), and 14 of 28 patients (combination). Side effects leading to an interruption of therapy were more frequent in the combination group than in the monotherapy arms.**

Conclusion: **This prospective, randomized, multicenter study shows for the first time that somatostatin analogs, interferon alfa, or the combination of the two had comparable antiproliferative effects in the treatment of metastatic neuroendocrine gastroenteropancreatic tumors. Response rates were lower compared with those published in previous, nonrandomized studies. The antiproliferative effect of the tested substances was similar for functional and nonfunctional neuroendocrine tumors.**

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NEUROENDOCRINE GASTROENTEROPANCREATIC tumors, formerly also called carcinoids or APUDomas, are characterized by slow growth as well as specific symptoms (eg, flush and secretory diarrhea) and syndromes (eg, Zollinger-Ellison and carcinoid syndrome). Neuroendocrine tumor cells secrete a variety of (poly-) peptide hormones, neuropeptides, and neurotransmitters, which cause the typical hypersecretion-related symptoms and syndromes in approximately half of all cases. Whereas functional, hormone-active neuroendocrine tumors do not differ from their nonfunctional, hormone-inactive counterparts in prognostic and therapeutic terms, several studies suggest that the location of the primary tumor affects the functionality as well as the clinical course of the disease.[1] For example, metastatic neuroendocrine tumors with primaries located in the pancreas and duodenum secrete mainly (poly-) peptide hormones (eg, gastrin, insulin, or vasoactive intestinal polypeptide), whereas primaries located in the jejunum, ileum, and coecum cause symptoms related mainly to the excessive release of biogenic amines (eg, serotonin) and neuropeptides (eg, tachykinins).[2] In contrast, metastatic neuroendocrine tumors located in the distal colon and rectum are not functional. On the basis of these observations and the variable prognosis, which is related to the primary location, neuroendocrine tumors of the gastroenteropancreatic system have been subdivided into foregut (stomach, pancreas, and duodenum), midgut (jejunum, ileum, and coecum), and hindgut (left colon and rectum) tumors. On the basis of these

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well-established clinical phenomena as well as our current expanding knowledge on neuroendocrine tumor biology shared by most of these well-differentiated tumors, an international board of pathologists has suggested a new classification of (neuro-) endocrine tumors.[3] This classification has been approved by the World Health Organization (WHO) and has already gained broad acceptance in neuroendocrine tumor pathology.

Clearly, surgical curative treatment of neuroendocrine tumor disease can only be achieved in patients with small primary neuroendocrine tumors or tumors with limited local disease. Curative treatment is more often achieved in hormone-active functional disease, because specific hypersecretory symptoms cause patients to seek medical advice at an earlier stage.

For inoperable, well-differentiated, metastatic neuroendocrine tumors, biotherapy with somatostatin analogs or interferon alfa represents the treatment of choice.[4,5] Therapy serves two purposes: first, to control symptoms in functional tumor disease, and second, to control tumor proliferation. An antiproliferative action has been reported in both functional as well as nonfunctional tumor disease.[6-10] Chemotherapy, including streptozotocin and fluorouracil or doxorubicin, has been recommended, especially in patients with pancreatic neuroendocrine tumors that progress with biotherapy. Chemotherapy has been restricted to well-differentiated tumors of the foregut, which are relatively sensitive to chemotherapy, and the rare, undifferentiated neuroendocrine tumors. The latter tumors seem to be unresponsive to biotherapy.[11,12]

First-line treatment of functional metastatic neuroendocrine tumors requires the control of excessive hormone activity (ie, the neuroendocrine hypersecretion syndromes) using secretory inhibitors such as somatostatin analogs (eg, octreotide or lanreotide) or interferon alfa.[4,5,13]

In addition, given the observed antiproliferative effects of these antisecretory substances in vitro and in vivo, biotherapy has also been suggested for both functional as well as nonfunctional progressive metastatic neuroendocrine tumors.

Several retrospective studies have suggested that the antiproliferative effects of somatostatin analogs or interferon alfa alone can be further enhanced if a combination of the two is used.[14-18] However, all studies reported so far have been performed in a nonrandomized, retrospective fashion in only a small number of patients.

Therefore, according to established standards of medical evidence, we initiated a prospective, randomized, multicenter study in therapy-naive patients with metastatic neuroendocrine gastroenteropancreatic tumors to investigate both the antiproliferative and symptom-controlling effects of the somatostatin analog lanreotide and interferon alfa as single agents and in combination.

On the basis of clinical experience by a substantial number of centers, somatostatin analogs seem to be more effective in comparison with interferon alfa because of fewer side effects and a possibly higher antiproliferative action. Given this experience, the hypothesis of our study was that the 1-year progression-free survival rate in patients with progressive metastatic neuroendocrine tumors treated with interferon alfa is lower than the corresponding rate for patients treated with lanreotide and that the combination of lanreotide and interferon alfa is superior to the corresponding monotherapies.

METHODS

Protocol

During an observation period of at least 3 months before entry into the study, each patient had documented tumor progression according to WHO criteria[19] as judged by computed tomography (CT) scanning of the abdomen or abdominal ultrasound.

Surgical removal of the primary tumor in the case of small and localized tumors as well as surgical alleviation of any obstructive symptoms was performed in all patients at the beginning of their neuroendocrine tumor disease. The patients had had no other previous antiproliferative or tumor reduction treatment.

The criteria for exclusion were an Eastern Cooperative Oncology Group performance score of 3 or 4, previous therapy for more than 4 weeks with any of the study agents, any chemotherapy or chemoembolization of liver metastases, a leukocyte count less than 2.5×10^9/L, or a platelet count less than 100×10^9/L. Patients were also excluded if they had any other concurrent or recent malignant disease.

Lanreotide (Ipsen Biotech, Paris, France) was given at a dose of 1 mg three times a day by subcutaneous injection. Interferon alfa (Intron A; Essex Pharma, München, Germany) was administered at a dose of 5×10^6 U three times a week by subcutaneous injection. Combination therapy consisted of the same dosages of lanreotide plus interferon alfa.

Patients showing progressive disease while receiving the initially assigned treatment with lanreotide alone or interferon alfa alone received the combination of lanreotide and interferon alfa.

The primary end point was the 1-year tumor progression rate. Secondary end points were symptom control (eg, flush, diarrhea) as well as biochemical response assessed by serum chromogranin A levels, serum serotonin levels, and urinary 5-hydroxyindoleacetic acid (5-HIAA) levels. To standardize the serum chromogranin A test and to avoid assay variations, chromogranin A from all different centers was sent to one reference laboratory.[20]

All patients were re-evaluated every 3 months by transabdominal ultrasound and CT scans, including oral and intravenous contrast enhancement. The size of a measurable indicator lesion as well as the size and number of liver and lymph node metastases were estimated. The tumor response was classified according to WHO criteria[19]: complete response was defined as a complete disappearance of all tumor lesions, partial response was defined as a 50% reduction in the product of perpendicular tumor diameters without appearance of new metastases, stable disease was defined as less than a 50% reduction but no greater than a 25% increase in the product of perpendicular diameters, and progressive disease was defined as more than a 25% increase in the product of perpendicular diameters or the appearance of new metastases. All critical cases were re-reviewed by an independent radiologist.

The sample size calculations were based on the following reasoning: The 1-year progression-free survival rate is 25% for lanreotide, 15% for interferon alfa, and 45% for the combination therapy. On the basis of a trend test for proportions, a group size of 35 patients is needed to establish a difference between groups on the level of 5% and with a power of 80%.

The statistical analysis of disease progression was based on a linear-by-linear association test and a multivariate logistic regression model (to take into account the stratified nature of the study) to evaluate the relation to treatment groups. To handle drop-outs, imputation methods were used to complete the 1-year observation.[21] The success of the randomization was assessed by applying the χ^2 test as well as the Kruskal-Wallis test to characteristics of the patients and the disease. Unadjusted medians for the length of time to tumor progression were estimated from Kaplan-Meier life-tables curves.

Patients were enrolled onto this trial (July 1995 through October 1998) after giving written informed consent. The protocol was approved by the ethics committee in each medical center.

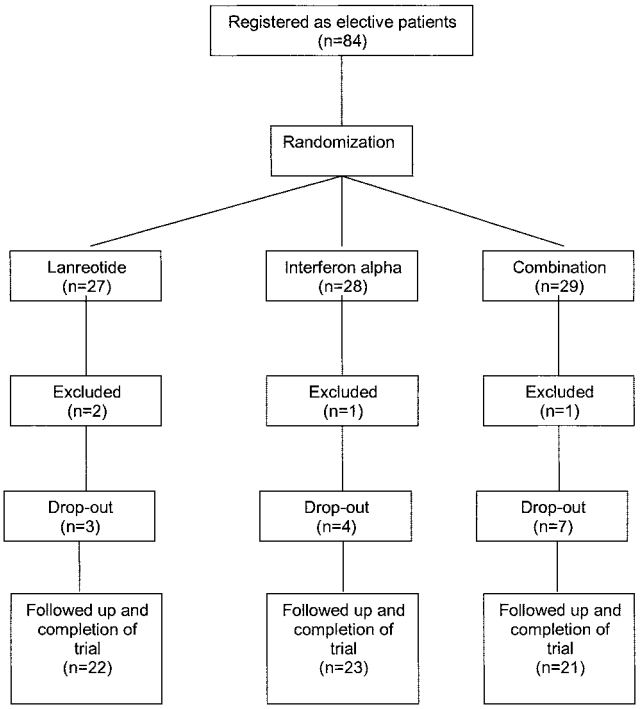

Fig 1. Trial profile.

Assignment

Patients were stratified according to the localization of the primary tumor (foregut, midgut, hindgut, unknown) and according to whether their tumor was functional or nonfunctional. They were then randomly assigned to therapy with lanreotide alone, interferon alfa alone, or the combination therapy with lanreotide plus interferon alfa. A stratified block-wise randomization with block size 6 was carried out centrally by telephone using randomization tables.

Masking

There was no masking performed. The study was open.

Role of Funding Source

Ipsen Pharma and Essex Pharma, in collaboration with the key investigators, participated in the development of the study design, provided funding, and participated also in the collection of the data. Analysis and interpretation of data and writing of the report was performed independently of the two pharmaceutical companies. Ipsen Pharma and Essex Pharma and the authors agreed at the outset to publish the results of this study at the earliest available opportunity.

RESULTS

A trial profile is provided in Figure 1.

Between July 1995 and October 1998, 84 patients were registered and enrolled onto the study. Eighty patients had a progressive neuroendocrine tumor disease with a histologically proven well-differentiated neuroendocrine tumor and were observed until the end of the study. Four patients (two in the lanreotide group, one in the interferon group, and one in the combination group) had to be excluded after randomization.

The primary localization of the tumor was in the foregut (36 patients: 26 pancreatic endocrine tumors, five bronchial, three gastric, one duodenal, and one common bile duct neuroendocrine tumor), midgut (30 patients), and hindgut (three patients). In 11 patients, the primary tumor location could not be identified. The majority of the patients (51 of 80) were nonfunctional, ie, no hypersecretion syndrome was observed. Twenty-nine patients had functional neuroendocrine tumors with a carcinoid syndrome. All of them had midgut tumors (so-called classical carcinoids). No patients with metastatic gastrinomas, insulinomas, vasoactive intestinal polypeptide tumors, or somatostatinomas were included in the study. Twenty-five patients were treated with lanreotide, 27 patients were treated with interferon alfa, and 28 patients were treated with lanreotide plus interferon alfa. Patients who experienced disease progression while receiving monotherapy were treated with combination therapy (n = 11). As shown in Table 1, patients were well matched among the

Table 1. Characteristics of the Study Patients

Characteristic	All Patients		Lanreotide		Interferon-Alfa		Combination	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Patients	80	100	25	31.3	27	33.7	28	35.0
Sex, male/female	47/33		12/13		17/10		18/10	
Median age, years	57.8		60.1		55.6		57.7	
Localization of the primary								
Foregut	36	45.0	14	56.0	10	37.1	12	42.9
Midgut	30	37.5	8	32.0	11	40.7	11	39.3
Hindgut	3	3.8	0	0	1	3.7	2	7.1
Unknown	11	13.7	3	12.0	5	18.5	3	10.7
Functionality								
Functional	29	36.3	12	48.0	9	33.3	8	28.6
Nonfunctional	51	63.7	13	52.0	18	66.7	20	71.4
Endocrine pancreatic tumors	26	32.5	9	34.6	8	30.8	9	34.6
Classical carcinoids	29	36.2	8	27.6	11	37.9	10	34.5
Previous surgical resections	41	51.2	14	56.0	12	44.4	15	53.6
Liver metastases	73	91.3	23	92.0	25	92.6	25	89.3
Other metastases	43	53.7	11	44.0	16	59.2	16	57.1
Octreoscan-positive	63/70	90.0	19/22	86.4	19/23	82.6	25/25	100

Table 2. Response to Therapy According to Treatment Group

	Partial Remission		Stable Disease		Progressive Disease		Drop Out (side effects)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Lanreotide	1/25	4.0	7/25	28.0	14/25	56.0	3/25	12.0
Interferon-alfa	1/27	3.7	7/27	25.9	15/27	55.6	4/27	14.8
Combination	2/28	7.1	5/28	17.9	14/28	50.0	7/28	25.0
Σ	4/80	5.0	19/80	23.8	43/80	53.7	14/80	17.5

treatment groups. Follow-up information was available for all patients for at least 12 months.

Results of Treatment

Among the 80 eligible patients who underwent treatment, all of them had serial measurements adequate to determine their response. After a 12-month study period, partial tumor remission as determined by CT or transabdominal ultrasound occurred in one of 25 patients in the lanreotide arm, one of 27 patients in the interferon alfa arm, and two of 28 patients in the combination arm. Inhibition of tumor growth leading to a stabilization of the tumor size (stable disease) was observed in seven of 25 patients in the lanreotide arm, seven of 27 patients in the interferon alfa arm, and five of 28 patients in the combination arm (Table 2). Within 12 months of therapy, tumor progression was observed in 14 of 25 patients (lanreotide), 15 of 27 patients (interferon alfa), and 14 of 28 patients (lanreotide plus interferon alfa; $P = .69$, linear-by-linear association test; $P = .71$, stratified logistic regression, imputation procedure). No complete tumor remission occurred. Because of ongoing tumor progression, six patients died during the 12-month study period. There was no significant difference in rates of partial remission, stable disease, or tumor progression among treatment groups. As shown in Fig 2, the length of time to tumor progression did not increase in patients treated with the combination of lanreotide and interferon alfa as compared with patients treated with interferon alfa or lanreotide alone. By contrast, patients with both a functional and nonfunctional midgut neuroendocrine tumor showed a statistically significant prolonged length of time to tumor progression compared with neuroendocrine tumors of the foregut ($P = .039$, log-rank test; Fig 3). The length of time to tumor progression was equal in patients with functional and nonfunctional tumors ($P = .472$, log-rank test; Fig 4).

Eleven patients who experienced disease progression while receiving monotherapy were treated consecutively with combination therapy after the failure of their originally assigned treatment with lanreotide (n = 4) or interferon alfa (n = 7) alone. Only one of these patients, pretreated with lanreotide, showed a clear reduction in the rate of tumor growth after changing to combination therapy.

Aside from the primary end point of this study, ie, the evaluation of objective response, the symptomatic and biochemical response was studied in parallel in 29 patients with functional neuroendocrine tumors. The frequency of the tumor-related symptoms, diarrhea and flush, in patients with functional neuroendocrine tumors decreased under therapy in each therapeutic group (Fig 5). Although a reduction of symptoms was observed in all therapeutic arms, a statistically significant reduction was only observed in the combination arm ($P = .037$, Wilcoxon test).

A biochemical response with a decrease in the corresponding neuroendocrine markers was observed in the patients with functional tumors. The decrease of the serum serotonin levels after a 3-month treatment period was statistically significant in every treatment group (all patients, 1,219 ± 951 μg/L *v* 730 ± 404 μg/L; lanreotide, 1,106 ± 876 μg/L *v* 814 ± 356 μg/L; interferon alfa, 1,697 ± 905 μg/L *v* 851 ± 402 μg/L; combination, 960 ± 1,070 μg/L *v* 561 ± 432 μg/L). Because of a wide spread of the chromogranin A levels in the individual patients,

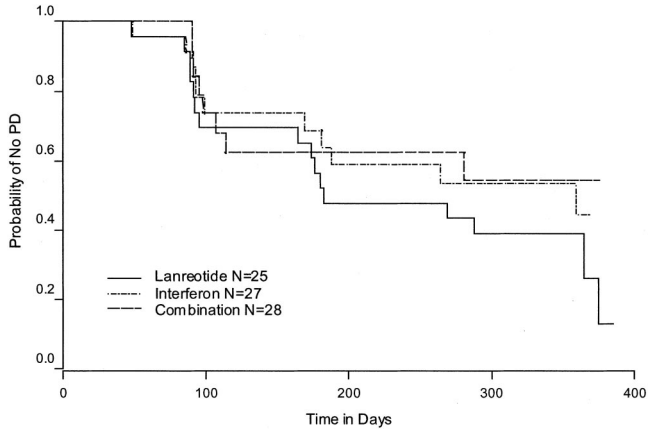

Fig 2. Time to tumor progression according to treatment groups (Kaplan-Meier estimates, log-rank $P = .312$).

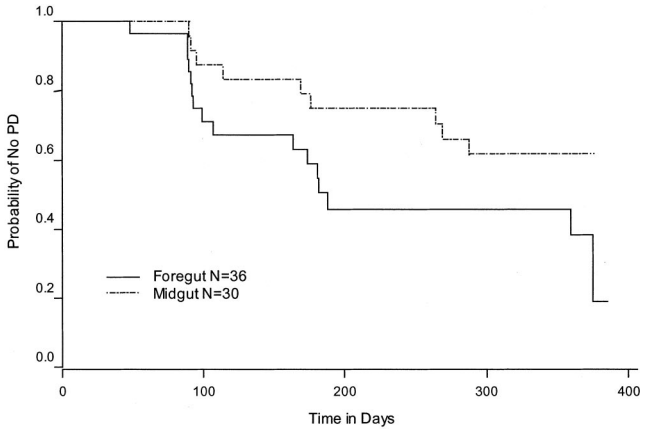

Fig 3. Time to tumor progression according to primary tumor localization (Kaplan-Meier estimates, log-rank $P = .039$).

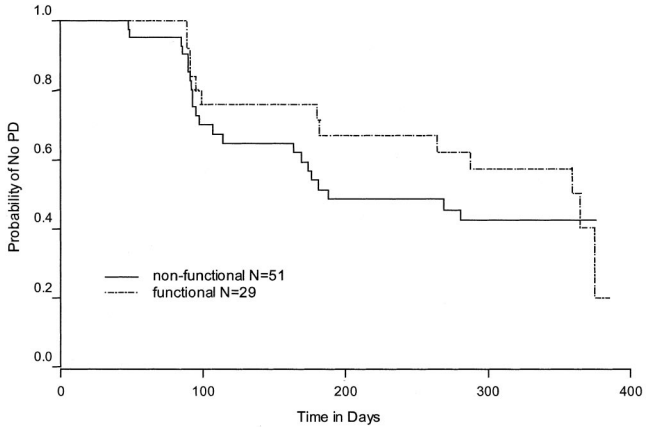

Fig 4. Time to tumor progression according to functionality (Kaplan-Meier estimates, χ^2 test, $P = .472$).

this marker demonstrated no clear correlation to therapy, although the decrease in serum chromogranin A levels was almost significant after a 3-month treatment interval in each treatment group (all patients, 8,915 ± 26,815 μg/L *v* 8,172 ± 23,563 μg/L; lanreotide, 1,125 ± 1,813 μg/L *v* 1,057 ± 1,640 μg/L; interferon alfa, 12,869 ± 21,172 μg/L *v* 6,441 ± 9,357 μg/L; combination, 18,132 ± 39,399 μg/L *v* 15,444 ± 43,022 μg/L). The differences in the 24-hour urinary 5-HIAA levels before and after treatment were not statistically significant. In general, biochemical response did not differ among the treatment groups and was not correlated with inhibition of tumor growth.

Side Effects

Treatment with lanreotide was generally well tolerated and only a few minor side effects occurred. Interferon alfa–related side effects were more common than those attributable to lanreotide (Table 3).

Table 3. Number of Side Effects According to the Treatment Groups

	Lanreotide (n = 25)	Interferon Alfa (n = 27)	Combination (n = 28)
Increase of liver enzymes	5	7	9
Diarrhea	1	—	3
Nausea	3	—	2
Pain (abdominal/at injection site)	6	1	4
Fever	—	3	3
Steatorrhea	2	—	1
Fatigue	1	1	—
Dyspnea	—	—	1
Depression	—	3	—
Allergic reaction	—	—	1
Gallstones/sludge	—	1	4
Headache	—	2	—
Alopecia	—	2	2
Hyper/hypoglycemia	4	2	4
Thyroiditis	—	1	1
Thrombocytopenia	—	1	1
Σ	22	24	36

Side effects leading to an interruption of therapy were more frequent in the combination group (seven of 28 patients) and to a lesser extent in the monotherapy arms (four of 27 patients who received interferon alfa and three of 25 who received lanreotide), leading to a prolonged time in study in the monotherapy arms (Fig 6). However, with respect to time in study, the difference between treatment groups was not statistically significant ($P = .337$, Kruskal-Wallis test).

Recruitment of patients was partly reduced because of an initial overestimation of recruitment capacities of the international partner as well as an underestimation of the number of available therapy-naive patients. Therefore, some design changes were necessary with regard to the initial protocol.

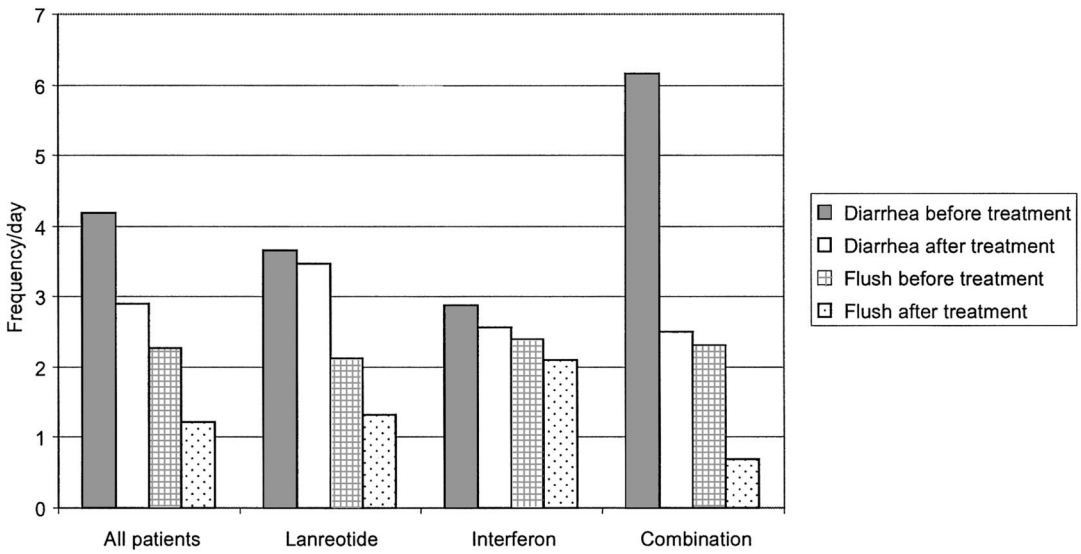

Fig 5. Development of the frequency of the diarrhea and flush symptoms in patients with functional neuroendocrine tumor according to the treatment groups after a 3-month treatment interval (all data given as mean).

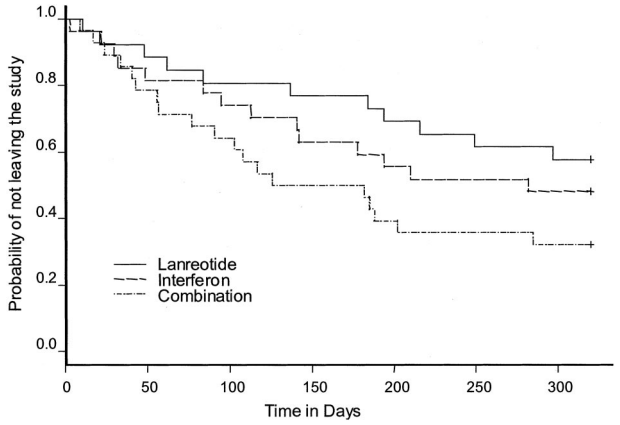

Fig 6. Time in study for the patients according to the treatment groups (Kaplan-Meier estimates, $P = .0337$, Kruskal-Wallis test).

DISCUSSION

The present study is the first prospective, randomized, multicenter trial evaluating the antiproliferative effect of monotherapy with a somatostatin analog (lanreotide) or interferon alfa and a combination of the two in patients with metastatic neuroendocrine gastroenteropancreatic tumors. Apart from surgery, all patients included in the study had had no previous antitumor treatment except for a maximum of 4 weeks of pretreatment with somatostatin analogs or interferon alfa and were therefore effectively therapy-naive. Before entering this study, all patients had documented tumor progression over an observation period greater than 3 months. Thus identification of therapeutic response in patients who experienced disease progression before study entry allowed assessment of true treatment effects between study arms.

All patients receiving lanreotide, interferon alfa, or both were studied for at least a 12-month follow-up period, indicating that a detailed evaluation of short- and long-term effects in responders could be evaluated. Similar to previous retrospective studies in smaller patient numbers as well as in meta-analysis,[4,8,10,22,23] no complete tumor response and only a few partial remissions were observed in our study.

As far as stable disease is concerned, response numbers are lower than those previously published. Reasons for this observation may be that (1) a relatively high number of foregut tumors (especially so-called endocrine pancreatic tumors in the older terminology) known to be less responsive than midgut tumors to biotherapy were studied, (2) response may have been overestimated by nonblinded radiologists in previous studies, (3) in the present study, lanreotide was used instead of octroetide, and (4) all patients included were therapy-naive, whereas in other studies therapy-naive patients were rare.

However, in contrast with other nonrandomized studies,[15-18] our study shows that the combination of lanreotide and interferon alfa had no higher antiproliferative effect than that of monotherapy with lanreotide or interferon alfa alone. The possibility of different types of neuroendocrine tumors in the previous reports supporting combination therapy could be one of the reasons for this controversial result in the present study. Only one of the 11 patients who were subjected to a cross-over from monotherapy to combination therapy after disease progression showed measurable inhibition of tumor growth. This single case is, however, in agreement with a recent study suggesting that addition of interferon alfa after failure of octreotide monotherapy may provide further antiproliferative efficacy.[18]

In contrast to foregut tumors, we observed higher rates of tumor growth inhibition in neuroendocrine midgut tumors in all three therapeutic arms. This confirms the long-standing hypothesis of a less favorable response of neuroendocrine foregut tumors to biotherapy. It may also be of interest for future use of biotherapeutics in progressive neuroendocrine metastatic gastroenteropancreatic tumors that response rates were identical for functional as well as nonfunctional tumors. This coincides with the finding that functional as well as nonfunctional neuroendocrine gastroenteropancreatic tumors follow a similar natural clinical course.

As far as control of hypersecretion-related symptoms is concerned, both lanreotide and interferon alfa gave a similar degree of control of the carcinoid syndrome. The combination of lanreotide and interferon alfa gave more control but an increased rate of side effects.

In our study, nearly all patients were examined by somatostatin receptor scintigraphy at study entry. Of the 70 patients studied, 63 were positive. As expected, all patients with midgut tumors were somatostatin receptor–positive (25 of 25 patients), whereas foregut tumors were only positive in 88% (30 of 34 patients). Patients with unknown primaries were positive in 66% (six of nine patients). Two patients with hindgut tumors were also somatostatin receptor–positive. Interestingly, receptor-negative patients showed a similar response rate as compared with the somatostatin receptor–positive cases, indicating that additional factors (eg, angiogenesis, lymphoid tissue, interference with, for example, growth factor secretion) other than the sole expression of somatostatin receptors in neuroendocrine tumor cells have to be considered as predictors for treatment effects.

Thus these findings do not completely agree with the concept that the effect of somatostatin analog therapy correlates with the (over-)expression of somatostatin-receptor subtype (sst) 2 or sst 5 in neuroendocrine gastroenteropancreatic tumor tissues[24,25] and that activation of sst 2 leads to an antiproliferative response.[26] Nevertheless, the somatostatin analog–mediated antiproliferative effect on neuroendocrine tumor cells seems to be dose-dependent. Dose-related tumor response to octreotide and other somatostatin analogs have not only been demonstrated in a variety of experimental tumor models, including pancreatic, breast, prostate, and lung cancer,[27-31] but also in some clinical studies.[9,32,33]

The mechanism whereby interferon alfa inhibits tumor growth in neuroendocrine cells has been recently elucidated, demonstrating direct effects of interferon alfa on the cell cycle with a prolongation of the S phase in neuroendocrine cells.[34] This mechanism could be responsible for the stable disease achieved in some of these patients. A possible reduction of viable tumor cells within metastatic lesions followed by an increase of fibrotic tissue[35] and antiangiogenic effects[36] has been also postulated as

a possible mechanism of the antitumor action of interferon alfa. So far, however, direct, convincing, experimental evidence demonstrating apoptosis of human neuroendocrine tumor cells in vivo is still lacking.

Concerning the influence of treatment on biochemical markers such as hormones and neurotransmitters, as expected, a biochemical response (especially for serum serotonin) with a decrease in the corresponding neuroendocrine markers was observed in the patients with functional tumors. However, biochemical response was not correlated with clinical response. This confirms the findings of some studies,[18] but not of others.[5] In contrast to the serum serotonin levels, the serum levels for chromogranin A showed only a weak correlation to the clinical response to treatment. Probably, this could be explained by new findings on the molecular mechanism of chromogranin A secretion in neuroendocrine tumor cells (Mergler et al, manuscript submitted for publication).

In summary, our data show, in contrast with previous nonrandomized studies, that biotherapy with interferon alfa and somatostatin analogs in therapy-naive patients with metastatic neuroendocrine gastroenteropancreatic tumors leads to either partial or complete tumor responses in only a minority of cases. However, in approximately one fourth of all patients (with documented tumor progression before biotherapy), stable disease can be observed. Combination of lanreotide and interferon alfa has no significantly higher antiproliferative effect than monotherapy with lanreotide or interferon alfa, and control of symptoms is better, but side effects are more common, under combination therapy.

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APPENDIX

The appendix is included in the full text version of this article only, available on-line at www.jco.org. It is not included in the PDF version.

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