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AN UPDATE OF THE MEDICAL TREATMENT OF MALIGNANT ENDOCRINE PANCREATIC TUMORS

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In the present study, we have updated our results with chemotherapy, α-interferon, octreotide and combinations of treatment modalities in patients with malignant endocrine pancreatic tumor (EPT). In our patient material of 134 EPT, 92 subjects had malignant tumors as evidenced by the presence of metastases or growth into adjacent organs. Seventy-eight patients had liver metastases. Streptozotocin plus 5-fluorouracil produced objective responses in 17/31 (54%) patients with a median duration of response of 23 months. The use of 5-HT3-antagonists as antiemetics has dramatically improved the quality of life during treatment by reducing the frequency of nausea to only 12.5%. The objective response rate to α-interferon (α-IFN) treatment, given as first-line treatment in 29 patients and after chemotherapy in 28 patients, was 51% (29/57) with a median duration of response of 20 months. Octreotide, which is still used as third-line treatment in most patients, produced significant biochemical responses in 6/19 (31%) patients with a median duration of 16 months. Combinations of α-IFN plus chemotherapy and a α-IFN plus octreotide in a small number of patients might indicate additive or synergistic effects. The median survival from start of treatment in the 92 malignant cases was 56.5 months, and for those with liver metastases (n = 78) at start of treatment 50 months. In conclusion, there are at least three effective therapies for malignant EPT and by combining them simultaneously or consecutively, a median survival of more than four years can be obtained.

Among malignant tumors, endocrine pancreatic tumors (EPT) represent a small but therapeutically very challenging group. New therapeutic options have recently been introduced (α-interferons and somatostatin analogs) (1, 2) in addition to standard chemotherapy, i.e. combinations with streptozocin, and hepatic artery embolization in the management of these patients. The future will probably bring additional new tools, e.g. new somatostatin analogs, and increased knowledge about the mechanism of action of these various agents will provide us with more potent combinations.

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The clinical characteristics of EPT are well known with a whole range of hormonal symptoms of varying severity and the frequently—but not always—indolent growth of the tumors. A somewhat distressing fact is the persistently delayed diagnosis in most patients despite improved diagnostic radiological and biochemical methods. The age at diagnosis and, hence, the stage of the disease has not been altered in recent series (3) compared to series from the 1970's and 1980's (4, 5). The best result of treatment that can be hoped for in most patients is still only palliation. Thus, there is a need for a very balanced decision on measures to be taken in each individual case. The expected therapeutic efficacy of the treatment must be weighed against the side-effects.

Three years ago we presented our results with causal medical treatment of EPT (6). Additional patients have been included in our studies and we now wish to update the results with chemotherapy, α-interferon, octreotide and also report on the results with combinations in a small

number of patients. The side-effects of these treatment modalities were discussed thoroughly in our previous report (6) and will not be covered in detail here with the exception of new adverse effects not previously observed.

Material and Methods

Out of 134 patients (72 men and 62 women) with EPT, 30 of whom with MEN-1 and admitted between 1977 and 1992, 92 (13 with MEN-1) had malignant tumors as indicated by the presence of metastases outside the pancreas or growth into adjacent organs. Liver metastases were demonstrated in 78 patients. Fifty-nine of the 92 patients with malignant tumors were included in our previous report (6). Histologic confirmation of the diagnosis was obtained in all malignant cases. The median age at diagnosis was 54 years (mean 51.3, range 16–85 years) for patients with malignant EPT. All patients were classified according to their clinical syndrome, if mixed according to the dominant syndrome and if changed according to the initial syndrome. For further patients characteristics, see Tables 1 and 2.

In addition to routine investigations of the blood, all patients underwent careful biochemical evaluation with measurements of serum gastrin, pancreatic polypeptide (PP), human chlorionic gonadotropin (HCG)-a and beta, insulin, c-peptide, pro-insulin, calcitonin, plasma vasoactive intestinal polypeptide (VIP), glucagon, somatostatin, and chromogranin A + B (7) by radioimmunoassays earlier described. All patients had elevations of plasma chromogranin and consequently we had at least one tumor marker besides other demonstrated tumor markers to follow during treatment.

Table 1

Patients with endocrine pancreatic tumors with regard to syndrome, benign and malignant disease

Syndrome	n	Malignant	Benign
Insulinoma	32 (4)	16 (1)	16 (3)
Gastrinoma	39 (12)	21 (5)	18 (7)
Non-functioning*	42 (11)	35 (4)	7 (7)
WDHA	16 (3)	16 (3)	
Glucagonoma	4	3	1
Somatostatinoma	1	1	
Total	134 (30)	92 (13)	42 (17)

No. of patients with MEN-I within parenthesis

* One patient with hypercalcemia due to increased secretion of PTH related peptide is included in this group

Due to our previous finding (6) that the combination of streptozocin (STZ) and doxorubicin was inferior to STZ plus 5-fluorouracil (5-FU) (5), the latter combination has been preferred since 1989. Thus, STZ plus 5-FU was given as described before with an induction course of 0.5 g/m^2 of STZ intravenously for five days, followed by a maintenance dose of 1 g/m^2 every third week. 5-FU was given intravenously (i.v.) concurrently with STZ at a dose of 400 mg/m^2 for 3 days (induction) and then every third week. The interval between courses was increased to 6 weeks after 12 months of treatment. Altogether 31 patients have received this combination, 24 of them having received no prior treatment, whereas 7 patients had been treated with α-interferon (IFN). 5-HT3-antagonists have been employed as antiemetics in 16 patients ever since 1989.

By now, 57 patients have been treated with α-IFN, 28 of whom had received previous chemotherapy. As mentioned

Table 2

Patient characteristics

Charcteristic	STZ + 5-FU	α-IFN	Octreotide
No. of patients	31	57	19
Sex (M/F)	13/18	33/24	10/9
Median age at diagnosis years range	58 (20–85)	53 (20–78)	62 (41–78)
Time from diagnosis median (months)	6	33	32
Clinical syndrome			
Insulinoma	7	5	1
Gastrinoma	9	13	3
Non-functioning	10	25	6
WDHA	4	12	9
Glucagonoma	1	1	
Somatostatinoma		1	
No. of patients with liver metastases	26 (83%)	43 (75%)	18 (94%)
Previous treatment			
chemotherapy	–	28	12
α-IFN	7	–	16

before, human leukocyte IFN or natural IFN was used in our initial studies but from 1986 recombinant IFN-a2b (Introna, Schering Corp., USA) has been utilized. The maintenance dose of natural IFN was 6 MU daily and of Introna 5 MU three times a week subcutaneously (s.c.) or i.v.

Octreotide as a single agent has been used in 19 patients. Most patients have been started on 100 μg twice daily s.c. but the dose had to be increased in 15 patients to maintain the effect. We have recently tried high-dose continuous s.c. infusions of octreotide ($>3\,000$ μg/day) via Deltec pump in two patients who escaped control on the lower dose. All patients were provided with replacement of pancreatic enzymes from the start of octreotide treatment.

In addition, the combination of α-IFN and STZ plus 5-FU has been attempted in 5 patients: two patients with non-functioning tumors, one insulinoma, one gastrinoma and one glucagonoma patient, two of whom had responded to prior INF treatment and one had responded to STZ plus 5-FU. Four patients (three with the WDHA syndrome and one with a non-functioning tumor) have received the combination of α-IFN and octreotide, two of whom had received and responded to prior α-IFN treatment.

The overall median duration from diagnosis/or surgery until start of medical therapy was 6 months.

When being started on a new treatment modality, either the first or subsequent alternatives, all patients were in a stage of disease progression. They were considered to have an objective or partial response if all the circulating tumor markers and/or tumor mass, measured as the product of perpendicular diameters, decreased by more than 50%. Stable disease was defined as a less than 50% reduction in tumor markers and/or tumor size. Progressive disease was defined as an increase by at least 25% in tumor markers and/or tumor mass or the demonstration of new metastases.

Survival analyses were performed according to the Kaplan-Meier method.

Results

The results of treatment with STZ plus 5-FU, α-IFN, and octreotide are presented in Table 3.

Among the 31 patients who received STZ plus 5-FU, 17 (54%) responded objectively with a median duration of response of 23 months (range 3–68 months). Biochemical responses were noted in 15 patients (48%) and significant tumor regression in 11 (35%) patients. In accordance with earlier results, malignant insulinomas (71%) appeared to be more sensitive to STZ plus 5-FU than other tumors (about 50%). Notably, only four patients with the WDHA syndrome were included and two (50%) responded. Stable disease was noted in six patients (20%) for a median of 6 months. The most disabling side-effect of STZ treatment, nausea and vomiting, seen in 85% in the previous report has been much improved with the use of 5-HT3 receptor antagonists, being completely absent during all courses in 14/16 patients. The remaining two subjects suffered from nausea from the first course but never developed vomiting.

Out of 57 patients treated with α-IFN, 29 (51%) responded objectively with biochemical and radiological responses in 27 (47%) and 7 (12%) patients respectively. The median duration of response was 20 months (range 2–96 months). Patient with the WDHA 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 had received prior chemotherapy ($n = 28$) had a response rate of 55%, whereas previously untreated patients ($n = 29$) had a response rate of 44%.

Three patients who received Introna developed neutralizing antibodies, which resulted in a loss of therapeutic effect, but they responded again when natural IFN was given. Another previously not described adverse effect of α-IFN treatment was myositis with severely disabling muscular pain seen in one patient after only three months of treatment which necessitated withdrawal of treatment. Furthermore, polyneuropathy with painful dysestesia in the distal extremities developed in two patients after three years of IFN treatment. Tricyclic antidepressive medication improved the symptoms and IFN therapy could be continued.

Octreotide produced objective biochemical responses in 6 out of 19 patients (31%) with a median duration of response of 16 months (mean 16 months, range 2–30). No significant tumor regression was noted. Also in this study, patients with the WDHA syndrome responded best (5 out of 9 or 55%). Six patients (31.5%) showed stable disease with a median duration of 6 months.

Two patients (one gastrinoma and one with the WDHA syndrome), who had initial responses but developed tachyphylaxis to octreotide treatment, were attempted on high-dose octreotide (3000 μg/day) by continuous subcutaneous infusion. The attempt was successful in the patient with the WDHA syndrome but not as to the gastrinoma patient. Several patients have developed gallstones ($n = 5$) but none have had any clinically related symptoms despite continued treatment. Interestingly, the adverse effects did not deteriorate with high-dose octreotide.

Five patients received the combination of STZ plus 5-FU and α-IFN, three of whom having received α-IFN ($n = 2$) and STZ plus 5-FU ($n = 1$), but all showed signs of disease progression. In this group, three out of five responded, two of whom were earlier IFN-responders. The median duration of response was 11 months.

Four patients received the combination of α-IFN and octreotide, of whom two had received and responded to α-IFN but showed progressive disease. Three out of four patients responded objectively with a median duration of response of 21 months. Interestingly, it was possible to induce another durable response in the two IFN-responders with the combination. The third responder (with the

Table 3

Results of treatment

Syndrome	Total No.	Objective response			Stable disease	Progressive disease
		Overall	Biochem.	Radiol.		
Streptozocin + 5-FU						
Insulinoma	7	5	5	1	–	2
Gastrinoma	9	5	4	5	2	2
Non-functioning	10	5	4	3	3	2
WDHA-syndrome	4	2	2	2	1	1
Glucagonoma	1					1
Total	31	17 (54%)	15	11	6 (20%)	8 (26%)
Duration of response						
Mean 25.5 months						
Median 23 months						
α-Interferon						
Insulinoma	5	1	1		2	2
Gastrinoma	13	5	5	2	6	2
Non-functioning	25	11	10	2	6	8
WDHA	12	10	9	2	1	1
Glucagonoma	1	1	1	1		
Somatostatina	1	1	1			
Total	57	29 (51%)	27	7	14 (24.5%)	14 (24.5%)
Duration of response						
Mean 22.1 months						
Median 20 months						
Octreotide						
Insulinoma	1					1
Gastrinoma	3	1	1		1	1
Non-functioning	6				4	2
WDHA	9	5	5		1	3
Total	19	6 (31.5%)	6	0	6 (31.5%)	7 (37%)
Duration of response						
Mean 16.8 months						
Median 16.0 months						

non-functioning tumor) had a 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 diagnosis in the 92 patients with malignant tumors was 72 months and median survival from start of treatment (chemotherapy, α-IFN or octreotide) in the same group was 56.5 months (Fig. 1). Survival analysis was performed separately in the 78 subjects displaying liver metastases at the initiation of treatment and the median survival from start of treatment was found to be 50 months (Fig. 2). Patients with malignant functioning EPT had a median survival from start of treatment of 60 months compared to 40 for malignant non-functioning tumors ($p = 0.067$).

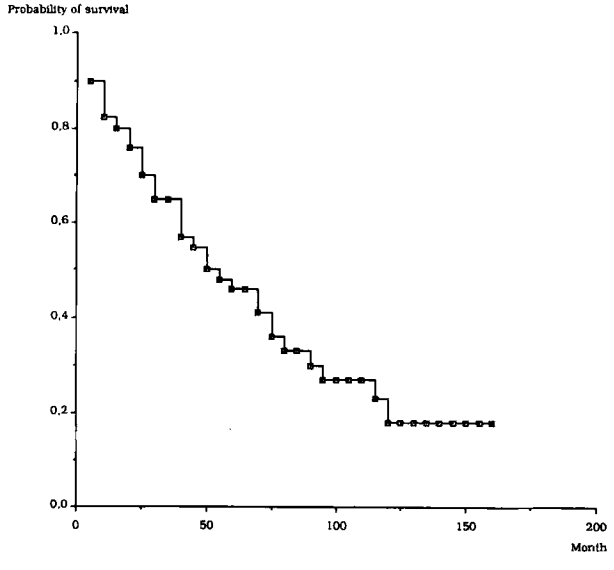

Fig. 1. Survival from start of medical treatment in patients with advanced malignant endocrine pancreatic tumors ($n = 92$). Median survival 56.6 months.

Discussion

Before discussing the medical treatment of EPT, it is interesting to notice that the composition of our patient

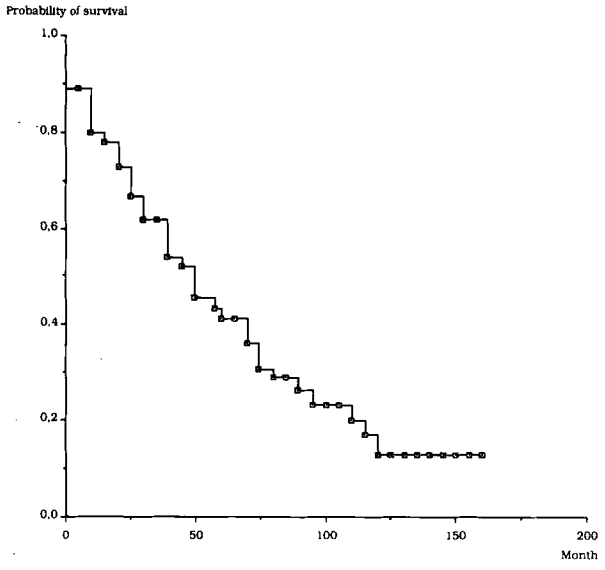

Fig. 2. Survival from start of treatment in patients with liver metastases (n = 78). Median survival 50 months.

material with regard to clinical syndrome has changed compared to our previous report (6). The proportion of patients with non-functioning tumors has increased from 23% to 33% and within this group the percentage of malignant tumors is also higher, 83% compared to 70%. There is no obvious explanation for this change but improved diagnostic procedures such as analyses of chromogranin A + B in plasma and in tumor tissues might have contributed.

Multiple hormone production is a well-recognized phenomenon in EPT, which sometimes makes it difficult to decide what clinical syndrome the patient should be assigned. One of our patients, for instance, had elevations of eleven different circulating tumor markers. Nevertheless, we consider that classification according to clinical syndrome is both necessary and relevant, as long as there is no better classification criterion, in order to render trials in different institutions comparable.

Our results with medical treatment in the present study differ somewhat from what we reported earlier. The response rate is not significantly different, 54% versus 58%, but duration of response for STZ plus 5-FU is shorter, 23 months as compared to 36 months. One possible explanation for the lower response rate could be the relatively small number of patients with the WDHA syndrome and the large number of non-functioning tumors included. Tumors associated with the WDHA syndrome are considered to be more sensitive to chemotherapy than non-functioning tumors. In agreement with earlier results, malignant insulinomas are the tumors most sensitive to chemotherapy.

The combination of STZ plus doxorubicin has not been utilized since 1988 due to our finding that this combination produced lower response rates than STZ plus 5-FU and was accompanied by more toxicity. In a recent study Moertel et al. (8), in contrast to our results, concluded that STZ plus doxorubicin was the superior combination, achieving both higher response rate (69%) and longer survival (median 2.2 years from start of treatment). However, it is impossible to compare the results since the classification of the patients in the ECOG study is not clear. Furthermore, almost half of the patients in each study group were not biochemically evaluated. One of the major drawbacks with the combination of STZ plus doxorubicin is the maximum dose of doxorubicin, which is often reached and should not be exceeded.

Whatever combination is the most efficient, both are active and have an established role in the management of patients with malignant EPT. After the introduction of 5-HT3 antagonists as antiemetics, STZ treatment has become much more tolerable for the patients. Only 12.5% of the patients, as compared to 85% in our previous report, developed nausea. This improvement is extremely important, since the treatment is only palliative and the quality of life is better.

In our initial studies with α-IFN, the obejctive response rates were about 70% (1). Our experience with this treatment modality has increased and by now 57 patients have been treated with α-IFN, half of them receiving α-IFN as first-line treatment. The objective response rate at present is about 50% with a median duration of response of 20 months. In the IFN-treated group, almost half of the patients had non-functioning tumors (25 out of 57; 44%) and 44% responded, whereas 83% of the patients with the WDHA syndrome responded. Insulinomas were even less sensitive than non-functioning tumors (one out of 5 patients had responded). Significant tumor regression was obtained in 14% of patients, which is in accordance with our earlier report.

The occurrence of neutralizing antibodies to recombinant α-IFNs has been recognized before (9) and even if it is not a common phenomenon (5%), it should be remembered, especially if IFN-related side-effects disappear and the suppressed leukocyte count normalizes. The therapeutic effect can be restored with natural IFN. Another not previously described autoimmune phenomenon disclosed in one of our patients is myositis. Myalgia with a slight and migrating muscular pain is a common adverse effect of IFN. The particular patient who developed poly-myositis had so severe muscular pain that she was almost immobilized. In addition, she had a high sedimentation rate (> 100 nm) and very high levels of myoglobin (> 1 200 μg/l). α-IFN treatment had to be discontinued and steroid treatment initiated. A polyneuropathy-like condition with disabling dysestesia in the distal extremities occurred in two patients but symtoms were alleviated with tricyclic agents and treatment could be continued.

Octreotide treatment produced objective biochemical responses in 31% of patients and no radiological responses,

which is similar to our previous findings. Whether high-dose octreotide is more effective than low-dose is impossible to say due to our limited experience (only two patients).

Combinations of cytotoxic drugs and α-IFN have been very useful e.g. in multiple myelomas (10). We tried the combination of STZ plus doxorubicin and α-IFN in 6 patients in our previous report, but this combination had no beneficial effects and rather worsened the side-effects. The combination of α-IFN and STZ plus 5-FU, used in 5 patients, was well tolerated and of them 3 responded. Due to the small number of patients it is difficult to say whether the combination is better than any of the single therapies.

An additive or synergistic effect of the combination of α-IFN and octreotide has been described in patients with malignant carcinoid tumors (11). The 4 patients with EPT who received this combination tolerated the treatment very well and 3 responded with a median duration of 21 months. The antitumor effect was dramatic in one of these patients, who could undergo curative surgery. Very few tumor cells, but increased fibrosis, could be seen in the tumor specimen.

Survival analysis showed a median survival from diagnosis of 72 months and a median survival from start of medical treatment of 56.5 months in malignant EPT ($n = 92$). For comparison, the median survival from start of treatment in patients with liver metastases ($n = 78$) was analyzed separately and was estimated at 50 months. There was a tendency to a longer survival from start of treatment for functioning tumors compared to non-functioning tumors but the difference was not statistically significant. In the ECOG study, the median survival from start of treatment for patients receiving STZ plus doxorubicin was 2.2 years. It is difficult to know whether or not the patient groups are comparable. Patient selection with regard to clinical syndrome and stage of the disease probably influences the result of treatment. In both our studies, however, patients were in a stage of progressive disease when treatment was started.

It is obvious that at present at least three effective therapies are existing and by combining these simultaneously or consecutively one can obtain a median survival of more than 4 years compared with 2.2 years when chemotherapy only was applied.

We consider that classification according to clinical syndrome is important but what is even more important is to find prognostic markers for a more malignant behavior that can be used among patients within a clinical syndrome. It is also important to use the predictive test for different therapies (2-5-A-synthetase and OctreoScan) (9, 12) that are available for an optimal management of these patients.

In conclusion, chemotherapy, α-IFN and octreotide have established therapeutic efficacy in malignant EPT. In the future, extended trials with combinations should be performed to increase the response rates. We also have great expectations for the new somatostatin analogs, somatuline (13) and octastatin (14), now being under investigation in our patients. Hopefully also other biological agents, such as retinoids, can act synergistically with α-IFN and improve the treament results in the future.

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