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Long-term results of continuous treatment with recombinant interferon-α in patients with metastatic carcinoid tumors—an antiangiogenic effect?

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This study investigated the efficacy of long-term continuous and dose-escalated interferon-α (IFN) treatment in patients with progressive carcinoid tumors. In this single-institution, phase II study 16 chemotherapy-naive, eligible patients were entered. Interferon treatment consisted on 5 MIU IFN three times weekly s.c. until radiologic progression. In case of progression the dose was increased to 10 MIU. Radiologic and biochemical evaluation was done monthly and thereafter 3 monthly. We have treated 16 patients of whom 15 are evaluable for tumor response. Calculated by standard response criteria, three patients experienced a partial response. Another three had an important minor response. Median response duration was 24 months (range 18–51 months). Biochemical responses were observed in nine out of 12 patients with an elevated 5-hydroxyindoleacetic acid excretion. The serum neuron-specific enolase proved a reliable marker for both response and progression. In the one patient progressive after 3 months, a dose increment to 10 MIU was without effect. In patients initially not progressing or responding to 5 MIU, escalation to 10 MIU had a short lasting beneficial effect in three cases. The radiological characteristics and the kinetics of these responses are compatible with an anti-angiogenic effect of IFN. This study of IFN in carcinoid tumors confirms the activity in this disease. Our results demonstrate the necessity of initiating treatment only in radiologically progressive patients and continuing this treatment until progression. We feel that currently the activity of IFN in metastatic carcinoid tumors compares favorably with that of systemic chemotherapy in patients with progressive disease.

Keywords: Angiogenesis, carcinoid tumors, interferon-α neuron-specific enolase.

Introduction

Carcinoid tumors are in general slowly proliferating neoplasms with, in most patients, only limited impairment of general well-being even in the presence of bulky metastatic disease.[1–4] However, they can produce and secrete a variety of biologically active peptides responsible for very diverse symptoms, sometimes leading to the carcinoid syndrome.[2,3] Another peculiarity of these tumors is their excessive stromal tissue production leading to the so-called 'desmoplastic' reaction, eventually responsible for clinical symptomatology, e.g. intestinal obstruction.[4] The occurrence of osteoblastic skeletal metastasis is also typical.[5] In different series the 5 year survival figures for patients with metastatic liver disease are around 20%.[4]

Treatment planning for these tumors should always include the consideration of surgical radical resection or debulking intervention. Current chemotherapy regimens are based on combinations with 5-fluorouracil, doxorubicin and streptozotocin.[2,4,6] These agents can produce responses in up to 30% but in general these effects are short-lasting. The treatment with interferon (IFN)-α has resulted in objective response rates ranging from 0 to 20% and biochemical responses from 25 to 65%. An identical wide variation has been reported for response duration.[4,7–17] The addition of chemotherapy to IFN failed to result in better response rates.[18,19]

In January 1989 we initiated a single-institution trial with continuous and escalating dose of recombinant leucocyte interferon; IFN-α2b (Intron®, Schering-Plough, Kenilworth, NJ) in patients with metastatic carcinoid tumors.

Patients and methods

Patient selection

Only untreated patients with measurable disease were entered in this study. Patients needed to have documented progressive disease, defined as a 25% increase in measurable lesions or the occurrence of new lesions over the last 3 months. Histology was reviewed in all instances.

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Routine phase II requirements with regard to cardiac, liver and renal function had to be fulfilled. Recent surgery or active infections were reasons for exclusion. Treatment with steroids or somatostatin analogs was not allowed.

Prior to initiation of treatment, three 24 h urine collections for 5-hydroxyindoleacetic acid (5HIAA) were obtained. Tumor response and biochemical response were assessed every 3 months. Plasma neuron-specific enolase (NSE) was measured in patients at 3-monthly intervals. This trial was approved by the Ethical Committee of the University Hospital Antwerp.

Treatment schedule

All patients were treated in an outpatient setting. Treatment with recombinant IFN-α was initiated with 5×10^6 IU by s.c. injection three times weekly. Most patients eventually learned to self-administer the drug. Patients continued treatment until progression at this dose level and then were treated with 10×10^6 IU again until progression. Once progression was observed at that dose, patients went off study. Acetaminophen was used preventively and routinely for palliation of fever and myalgia due to IFN. Biochemical or tumor marker evolutions were not considered arguments for either response or progression, and thus were not included in either dose-escalation decisions or treatment discontinuation.

Response assessment

Standard WHO criteria were used for toxicity assessment. An objective tumor response was considered a partial response once a 50% reduction in the sum of the products of the longest perpendicular diameters of all measurable lesions were observed. A minor response defined as a reduction of less than 50%, was also considered as proof of antitumor activity. This was considered reasonable in view of the slow rate of progression of these tumors. There could be no progression at any site nor could there be any new site of disease in this period. These changes had to last for at least 4 weeks. Criteria for no change or progressive disease were standard WHO criteria. A biochemical response was defined as partial by a fall of at least 50% of the initial 5HIAA value in three consecutive 24 h urine collections. A complete response was defined as normalization of excretion for at least 1 month.

Results

Patient characteristics

The clinical data are summarized in Table 1. All patients had measurable disease with a majority having liver metastasis. The term carcinoid syndrome was used if at least one symptom of either diarrhea, flushing or asthmatic bouts was present. In seven, both flushing and diarrhea were observed; in only one patient was the full clinical picture of the carcinoid syndrome present. This patient also suffered from symptomatic cardiac involvement. In 12 patients, 5HIAA excretion was consistently elevated in consecutive urine collection. The median pretreatment 5HIAA level in these patients was 75 mg/24 h with a range from 26 to 490 mg. The primary tumor was resected in only four patients. Most of them were diagnosed with widespread metastatic disease and presented with a tumor of unknown primary. Osteoblastic skeletal metastasis was seen in four patients.

Antitumor effect

Fifteen patients were evaluable for tumor response. One patient interrupted IFN treatment after 6 weeks because of worsening symptoms of congestive heart failure. He was considered inevaluable for response. We observed three patients with partial responses and three with minor responses (volume

Table 1. Patient characteristics.

Male/female	4/12
Median age	58(39–72)
PS	
0	2
1	9
2	4
3	1
Primary site	
lung	4
GI Tract	11
PTU	1
Site of metastasis	
lung	5
liver	11
bone	4
skin	1
brain	2
LNN	3
Carcinoid syndrome	8/16
5-HIAA	12/16
NSE	10/15

reductions of 38, 30 and 28%, respectively), resulting in an anti-tumor activity of 40% (95% confidence interval 16–64%) and a classical response rate of 20%. The median duration of IFN treatment before a partial response was documented was 24 weeks with a range of 12–30 weeks. The median duration of response was 29 months with a range of 12–51 months. Nine patients had a no change and one patient was progressive after 3 months on 5 MIU and also after another 3 months on 10 MIU, in spite of having a biochemical response.

Radiological changes

The radiological changes and the kinetics of these changes are shown in Figure 1. These show consecutive 3-monthly CT scans of one of the responding patients. These changes are remarkable in that prior to a substantial volume reduction a marked reduction of contrast enhancement occurs. Only months later was tumor size reduced. Progression was preceded by renewed contrast enhancement, prior to enlargement.

Biochemical responses and changes in tumor markers

Of the 12 patients with an increased 5HIAA excretion, nine had a partial or complete response as defined above. Only one patient had a transient increase in the excretion of the serotonin metabolite in spite of having an unchanged radiological assessment. The kinetics of this biochemical response was very variable with some patients having a normalization after 3 months. At the other extreme, was a patient with an initial 5HIAA excretion of 72 mg/24 h whose value dropped over a period of 36 months to around 12 mg/24 h. Due to substantial fluctuations in the excreted 5HIAA, this marked

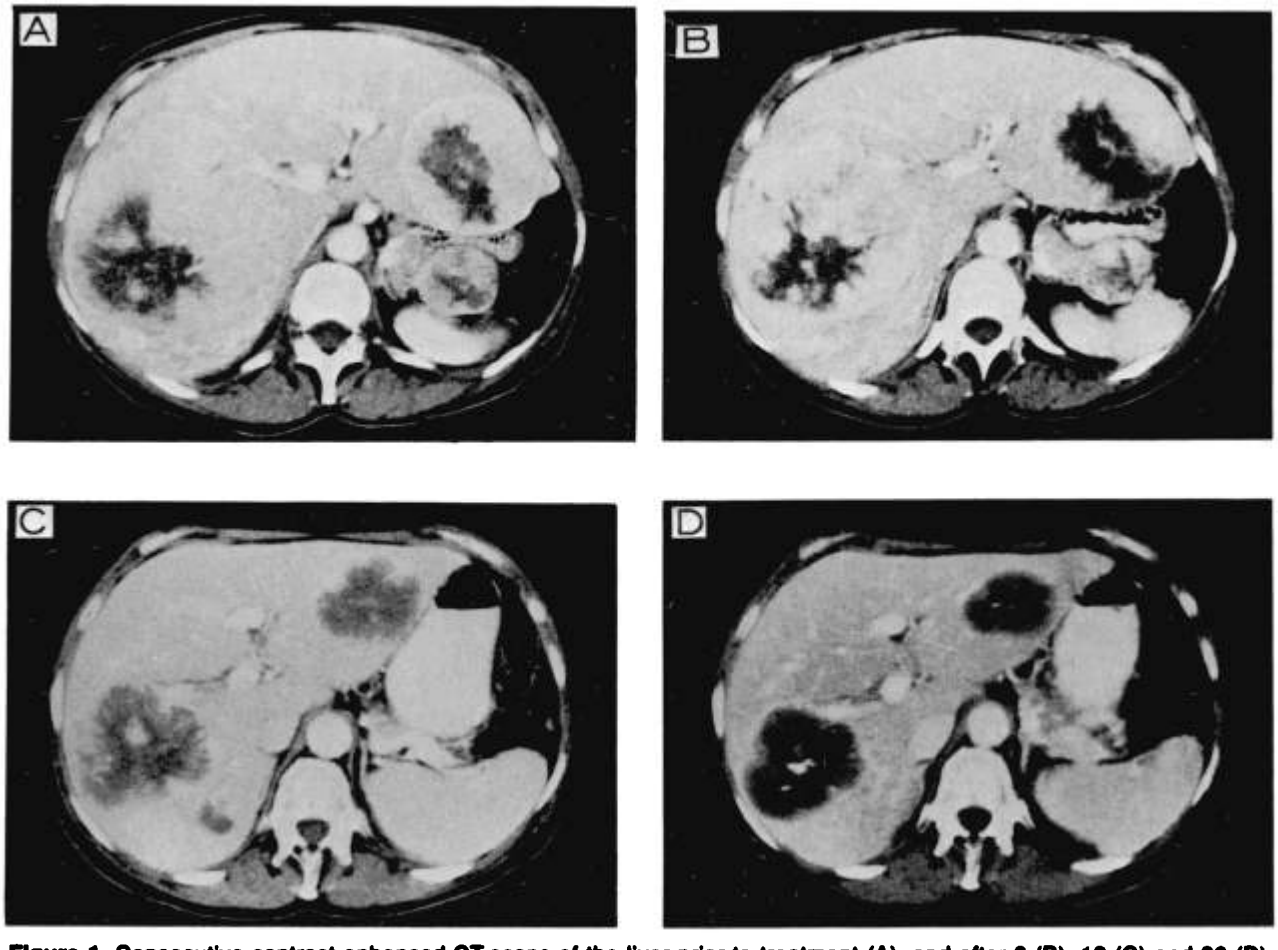

Figure 1. Consecutive contrast-enhanced CT scans of the liver prior to treatment (A), and after 6 (B), 12 (C) and 36 (D) months. This last scan shows early progression with renewed contrast enhancement.

Table 2. Tumor response.

Patient	Primary site	measurable lesion(s)	Time to response (weeks)	Response duration (months)	Type of response	Dose IFN (MIU)
W.E.	lung	lung	12	18	MR	5
V.M.Y.	PTU	liver	30	48	PR	10
V.P.M.	GI tract	liver	24	>24	PR	5
L.A.	GI tract	liver	24	21	MR	10
V.A.	GI tract	liver	24	51	PR	10
B.A.	GI tract	liver	12	>12	MR	5

proved unreliable in predicting tumor response or progression on radiology.

Ten patients had initially elevated serum NSE with a median of 20 ng/ml (range 17–125 ng/ml). There was no correlation with the presence or absence of 5HIAA excretion. Both tumor response and tumor progression were always preceded by a rise or fall in serum NSE levels. This marker proved much more reliable than 5HIAA excretion in predicting tumor behavior in spite of the relative moderate elevations of this marker in most of our patients. In 10 patients serum α-HCG was measured and found moderately elevated in four with values of 3.2, 3.6, 4.1 and 4.5 μg/l. There was no relationship in these four patients between tumor evolution and changes in serum α-HCG.

Toxicity

The toxic reactions are described in Table 3. Even despite the preventive use of acetaminophen, fever and chills, myalgia, and arthalgia continued to occur in many patients. These symptoms eventually subsided after continued treatment with IFN but in our experience this occurred only after several weeks and sometimes even months. In three patients the use of acetylsalicyc acid was needed to control fever. In two patients important neuro-psychiatric changes were observed. In a 46 year old woman with florid carcinoid syndrome and elevated serum serotonin levels, 4650 ng/ml, a rapid (after 1 months of therapy) and complete biochemical response was observed. This concurred with complete resolution of flushing and minor improvement of diarrhea, but also with emergence of a depressive state.

A second patient, who had been treated for the longest period, developed slowly progressive memory loss with eventually nearly complete loss of recent memory. On neuroradiological examination this was accompanied with aspecific changes. After interruption of IFN these memory problems clearly improved but without complete recovery of her mental capacities.

Table 3. Toxicity

Toxic effect	Number
Fever	14
Chills	1
Local reaction	2
Arthralgia	3
Myalgia	6
Fatigue	12
Anorexia	6
Disorientation	1
Depression	1
Anemia	
>10 g/dl	6
>8 g/dl	1
Leukopenia	
>3000/μl	4
>2000/μl	1
Thrombopenia	
>100 000/μl	4
>50 000/μl	0
Autoantibodies	
antinuclear antibody	4
antithyroid antibody	1
antipancreas antibody	1

We observed the development of autoantibodies in six patients. In one patient insulin-dependent diabetes mellitus developed with the presence of anti-pancreatic and anti-insulin antibodies. This patient also had local invasion in the tail of the pancreas by the tumor which might have contributed to these phenomena. This patient had no family history of diabetes.

Duration of response

From the 15 evaluable patients, one had progressive disease after 3 months on 5 MIU and further pro-

gressed on a dose of 10 MIU. He died 12 months after enrolment into this study. Fourteen patients, with initially documented progressive disease, continued treatment with a median follow-up of 42 months (range 22–60 months). Median time to progression in this group of 14 patients is 31 months (range 22–60 months).

Discussion

This study confirms earlier reports on the IFN sensitivity of carcinoid tumors.[7–19] This report describes in detail the kinetics of the IFN effect in these slowly progressive untreated patients. We have observed a response rate of 20% or even 40% depending on the criteria applied. We have never observed a substantial radiological antitumor effect prior to 12 weeks of treatment and sometimes only after 30 weeks of continued therapy. The observed responses, although slowly occurring, were long lasting. The biochemical response rate was substantial with nine of 12 patients having a more than 50% fall in the 24 h 5HIAA excretion.

The effect on symptoms was similar, with substantial improvement of flushing but with a more limited effected on diarrhea. Dose escalation in progressive patients after 3 months of 5MIU was without effect. The escalation of IFN to 10 MIU in those patients initially not progressing under 5MIU resulted in some short lasting beneficial effects.

The toxic effects of this treatment were predictable. We have also observed the relative frequent development of auto-antibodies, but this was in general without clinical consequences. In one patient insulin-dependent diabetes developed with the presence of anti-insulin and anti-pancreatic antibodies. This patient also suffered from local invasion of the tumor into the pancreatic tail. Her glucose intolerance and insulin requirements became much less once she further progressed and IFN treatment was stopped. The literature suggest that IFN might have some effect in this respect.[20–22] Two patients developed severe neurological toxicity. In general the other toxicities were mild and subsided after 1–2 months of therapy.

Over the past 10 years many reports have documented both biochemical and antitumor effects of human leukocyte IFN and of recombinant IFN-α. The response rates both for biochemical and for antitumor responses differ substantially between these reports. Even more surprising is the wide variation in response duration.

Several factors might help to explain these conflicting results. First, the possibility of patient selection and their pretreatment status might provide some explanation. In the Moertel study on 20 patients and using much higher dosages of IFN, an objective response rate based on tumor measurements of 20% was reported.[13] The radiological and biochemical antitumor effects were short lasting (7 and 4 weeks, respectively). The majority of these patients had been pretreated with chemotherapy. The rapid progression of these patients is somewhat surprising and differs from untreated patients with metastatic carcinoid tumors.

Secondly, the duration of treatment and dosing with IFN might be important. Some studies have interrupted treatment once no tumor response was observed after a predetermined period. We suggest to continue treatment of these patients until tumor progression occurs. In doing so we have observed definite antitumor effects only after 30 weeks of treatment. The 50% 'volume' reduction response criteria for the identification of active agents is in our opinion not suitable for slowly growing neoplasms. It is even less applicable if the agent under investigation is not a classic cytotoxic agent. Under these circumstances it makes more sense to use interruption of progression in patients with documented progressive disease.

The mechanisms of action of IFN in carcinoid tumors are unknown. Numerous studies, including this one, clearly demonstrate that significant objective tumor regressions can be obtained with this agent. Many different modes of action have been suggested.[23–25] Some suggest a modulation of cell cycle kinetics or a regulation of oncogene expression. Others suggest immune response modulation, including an effect on natural killer cells and macrophages. We suggest that an anti-angiogenic effect may be in part responsible for the observed effects. We think that several arguments are at hand to support this hypothesis. Firstly, the antitumor effect of IFN-α in solid malignancies is restricted to a limited number of tumor types.[26] Childhood hemangiomas, renal cell carcinomas and Kaposi's sarcoma are to a variable extent sensitive to IFN. All these tumors are highly vascular neoplasms, and all are known to contain and/or excrete angiogenic peptides such as basic-fibroblast growth factor (β-FGF) and vascular endothelial growth factor (VEG).[27,28] This is also true for carcinoid tumors and hemangiomas.[29–31] Secondly, the radiological changes in two patients with the most clear antitumor effects can be characterized by an initial decrease in contrast enhancement of the metastasis and is only later fol-

lowed by a further decrease in size and calcification of these lesions.

Others have used the contrast enhancement of lymph node metastasis in head and neck cancer as a predictive variable for response to chemotherapy, suggesting that this enhancement is a measure for vascularity.[31] These responses were slow to occur and were not accompanied by inflammatory symptoms such as in the case of other immune response modifiers. We consider all these effects to be suggestive of an additional anti-angiogenic effect of IFN in this disease.

The possibility of measuring angiogenic peptides might lead to reinitiating phase II studies with IFN-α in these diseases. This might result in superior patient selection and a more rational scheduling of this biological response modifier. Thirdly, the already described changes on consecutive MRI scanning and biopsies of liver metastasis of carcinoid tumors under IFN therapy show slow changes in tumor size but significant changes in tumor cell content.[33] These results are at least theoretically compatible with changes induced by an anti-angiogenic agent rather than caused by immune cell attack. Fourthly, the kinetics of the IFN effect take months before they lead to a radiological measurable change in dimensions. Similar kinetics are observed in the treatment of childhood hemangiomas with IFN.

The different treatment options for patients with metastatic carcinoid tumors should always include the possibility of surgery, the use of intrahepatic chemotherapy in combination with some form of hepatic dearterialization and the initiation of a somatostatin receptor blocking agent in conjunction with dietary measures in patients with a carcinoid syndrome. If, however, the use of systemic chemotherapy is being considered, we feel that the results obtained with IFN justify its use prior to cytotoxic agents. In our opinion IFN compares favorably both with regard to efficacy and toxicity.

In conclusion we confirm that activity of IFN in metastatic carcinoid tumors and suggest that this agent be used as first line treatment in patients with radiologically progressive disease. We think that several arguments are available to suggest a vascular target for the therapeutic effect of IFN in this disease. We are currently investigating this possibility in a prospective study.

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