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Treatment of Malignant Carcinoid Tumors: a Randomized Controlled Study of Streptozocin Plus 5-FU and Human Leukocyte Interferon

KJELL ÖBERG,* INGRID NORHEIM† and GUNNAR ALM‡*

**Ludwig Institute for Cancer Research, Uppsala Branch, University Hospital, Uppsala, †Department of Internal Medicine, University Hospital, Uppsala and ‡Interferon Laboratory at the Biomedical Center, Uppsala, Sweden*

Abstract—*In a randomized controlled study, 20 patients with malignant carcinoid tumors were included. Ten patients received streptozocin plus 5-fluorouracil for 6 months and another 10 human leukocyte interferon (IFN). After 6 months of treatment, an objective tumor response was noted in five of the patients treated with IFN (50%) but in none of the patients on chemotherapy. Stable disease was found in five patients (50%) on IFN treatment and four (40%) on chemotherapy. Progressive disease was noted in six of the patients (60%) receiving chemotherapy. A statistical analysis using the chi-square test showed a significantly higher proportion of responders and stable disease in the IFN treated group (P = 0.0039). Furthermore, three of eight patients who had previously received chemotherapy showed later on an objective response to IFN. The objective responses were mainly noted in decreased tumor markers; however, two patients also showed a significant reduction of tumor size. Subjective responses were noted in 72% of patients treated with interferon, but only in 9% of those treated with streptozocin plus 5-fluorouracil. The results indicate that interferon treatment is superior to the combination of streptozocin plus 5-fluorouracil. Considering both the therapeutic effects and adverse reactions, human leukocyte interferon is a promising alternative for treatment of patients with malignant carcinoid tumors.*

INTRODUCTION

NEUROENDOCRINE gut tumors, to which carcinoid tumors belong, show very variable responses to chemotherapy [1–3]. Streptozocin alone or in combination with 5-fluorouracil or Adriamycin® has demonstrated significant activity in patients with malignant endocrine pancreatic tumors with response rates of about 60% [1]. However, carcinoid tumors closely related to the former tumor type demonstrate lower response rates, 10–30% [2, 3]. From our own experience in 31 patients with malignant carcinoid tumors treated with the combination of streptozocin plus 5-FU, we could only get an objective response in 10% of the patients [4]. Human leukocyte interferon (IFN) has demonstrated significant effects on hormone levels and tumor growth in patients with malignant carcinoid tumors [5, 6]. In our long-term study [6], where 36 patients with malignant carcinoids were treated up to 42 months with IFN, we observed an objective response in 48% of the patients with 'mid-gut' carcinoid tumors and in three of four patients with lung carcinoids. The majority of the responses were noticed as a significant reduction of tumor markers, whereas four patients also demonstrated a significant reduction of tumor size. Furthermore two complete remissions were encountered. We have now performed a randomized controlled study of streptozocin plus 5-FU, the earlier 'standard' treatment, and human leukocyte interferon in 20 patients with malignant carcinoid tumors.

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Correspondence should be addressed to: Kjell Öberg, Ludwig Institute for Cancer Research, University Hospital, S-751 85 Uppsala, Sweden.

PATIENTS

Twenty consecutively referred patients with malignant carcinoid tumors were included in the study, 11 men and nine women, with a mean age of 61.5 years (range 46–70 years). The primary tumors were located in the ileum in 19 of the patients, whereas one patient had a bronchial carcinoid tumor. In all patients fresh tumor specimens were obtained and histologically examined for pre-

cise classification, using the Grimelius and Masson silver staining techniques [7, 8] as well as an immunocytochemical technique for detection of serotonin immunoreactivity. All patients presented symptoms of daily flushing and 17 patients also had diarrhea. Six patients had clinical signs of right heart failure which was confirmed by echocardiography. All patients were previously untreated.

All patients were subjected to computerized tomography and ultrasound investigation of the abdomen which showed liver metastases. These investigations were performed prior to the start of treatment and then repeated every 3rd month. Investigations of routine hematology, serum electrolytes, liver and renal functions were performed prior to every new course of chemotherapy and every 3rd month in patients on interferon treatment. Urinary 5-hydroxy indoleacetic acid (U-5-HIAA) was measured prior to treatment and then after 3 and 6 months using a method described earlier [9]. The mean value of two 24 h urine collections was used in the evaluation of the patients.

TREATMENT

Since the most important prognostic factor in carcinoid disease is the U-5-HIAA level the patients were primarily randomized according to this parameter to either chemotherapy (streptozotocin plus 5-fluorouracil) or interferon treatment. An equal number of patients with U-5-HIAA levels below or above 500 μmol/24 h (*cf.* range <80 μmol/24 h) were included in each arm of treatment. Other less important randomization parameters were sex and age.

Ten patients received human leukocyte interferon (Cantell type PIF A + B [10]) at daily subcutaneous injections of 6 MU. For an initial 3 days, half of that dose was given. Another 10 patients were randomized to treatment with streptozocin plus 5-fluorouracil. They received streptozocin as an intravenous bolus injection of 1 g on 3 consecutive days in combination with 5-fluorouracil 400 mg/m^2. The treatment was repeated every 6 weeks. This dose schedule of streptozocin plus 5-FU has been recommended by others [11, 12]. No other treatment for the carcinoid syndrome was used.

Evaluation of tumor responses

An objective tumor response was considered if the patient had more than 50% reduction of urinary 5-HIAA levels and/or more than 50% reduction of tumor size measured as the product of two perpendicular diameters on CT scan. Stable disease was designated as less than 50% decrease of tumor markers or tumor mass and no appearance of new metastases. A tumor progression was denoted as a more than 25% increase of the urinary 5-HIAA level or tumor size and/or occurrence of new metastases.

The daily number of flush attacks and episodes of diarrhea were monitored and evaluated in the subjective response.

STATISTICAL ANALYSIS

A chi-square analysis of the proportions of patients with tumor responses, stable and progressive disease was performed between the two treatment arms. We intended initially to include 30 patients, 15 in each treatment arm, in the study, but due to 'an early stopping rule' the material was analyzed in the interim of the 10 included patients in each arm. One treatment was outstanding and our statistician gave the advice to stop the trial after this analysis.

RESULTS

Treatment with streptozocin plus 5-fluorouracil (Fig. 1 and Table 1)

The 10 patients receiving chemotherapy had a median urinary 5-HIAA before start of treatment of 620 μmol/24 h (range 198–2705). After 6 months of treatment, none of the patients showed an objective tumor response either in markers or in tumor size, four (40%) showed stable disease and

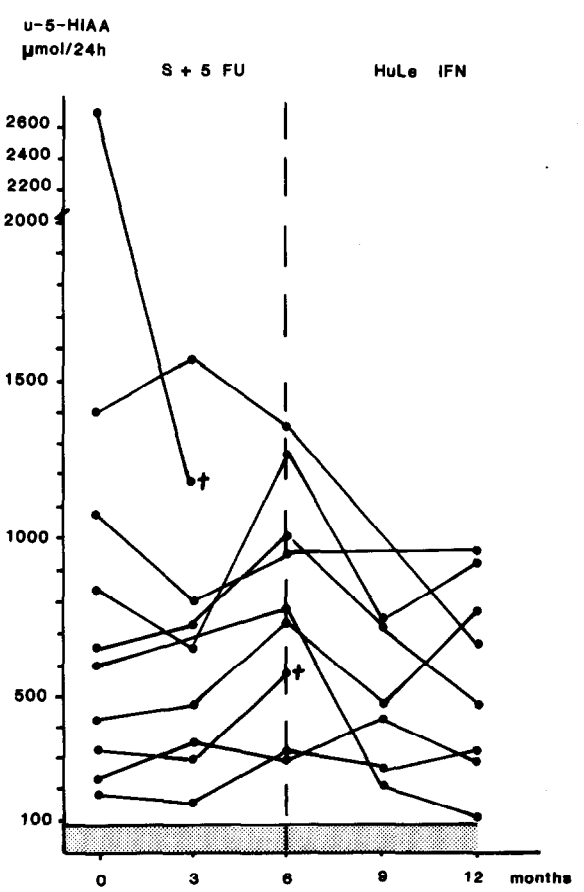

Fig. 1. Effects of streptozocin plus 5-fluorouracil and subsequently α-interferon on urinary 5-HIAA levels in 10 patients with malignant midgut carcinoid tumors. (+) indicates the death of the patient. Shaded area indicates reference range for urinary 5-HIAA (<80 μmol/24 h).

Table 1. *Evaluation of clinical responses at* 6 *months in patients with malignant carcinoid tumors, randomized to treatment with streptozocin plus* 5-*FU or interferon*

	Streptozocin + 5-FU	Interferon
Patient No.	10	10
U-5-HIAA (median)	620 μmol/24 h	680 μmol/24 h
'Clinical' responses		
Biochemical:		
OR	0	5
SD	5 (50%)	5 (50%)
PD	5 (50%)	0
U-5-HIAA (median)	640 μmol/24 h	390 μmol/24 h
Tumor size:		
OR	0	2 (20%)
SD	5 (50%)	5 (50%)
PD	3 (30%)	0
Subjective response:	1 (10%)	7 (70%)

six (60%) progressive disease. Median urinary 5-HIAA concentration after 6 months of treatment was 640 μmol/24 h (range 285–1375). One patient experienced a subjective improvement. One patient died from tumor progression and another patient died from right heart failure.

After 6 months treatment the remaining eight patients with stable or progressive disease were crossed over to interferon treatment and were reevaluated after a further 6 months.

Four of these patients had demonstrated stable disease on chemotherapy but after receiving interferon, two of them showed an objective tumor response and the other two continued to be stable. The other four patients had progressive disease on chemotherapy, but three of them became stable, and one showed an objective tumor response after receiving interferon. In total, three out of eight patients, unresponsive to chemotherapy, showed an objective response on interferon, and the others showed stable disease. None of the patients previously receiving chemotherapy progressed during interferon treatment.

Treatment with human leucocyte interferon (*Fig.* 2 *and Table* 1)

The 10 patients receiving interferon from the start of the trial showed a median urinary 5-HIAA concentration of 680 μmol/24 h (range 100–2300). After 6 months therapy, five patients (50%) showed an objective response and another five patients (50%) had stable disease. None showed progressive disease. The median 5-HIAA concentration after 6 months of interferon treatment was 390 μmol/24 h (range 48–2100). Seven patients showed subjective improvement (70%).

All the five patients displaying an objective tumor response, had a significant decrease of urinary 5-HIAA and two patients also had a significant reduction of tumor size. Two patients with stable disease died from right heart failure. One patient with stable disease crossed over to treatment with streptozocin plus 5-fluorouracil for 6 months and he continued to be stable also during this treatment.

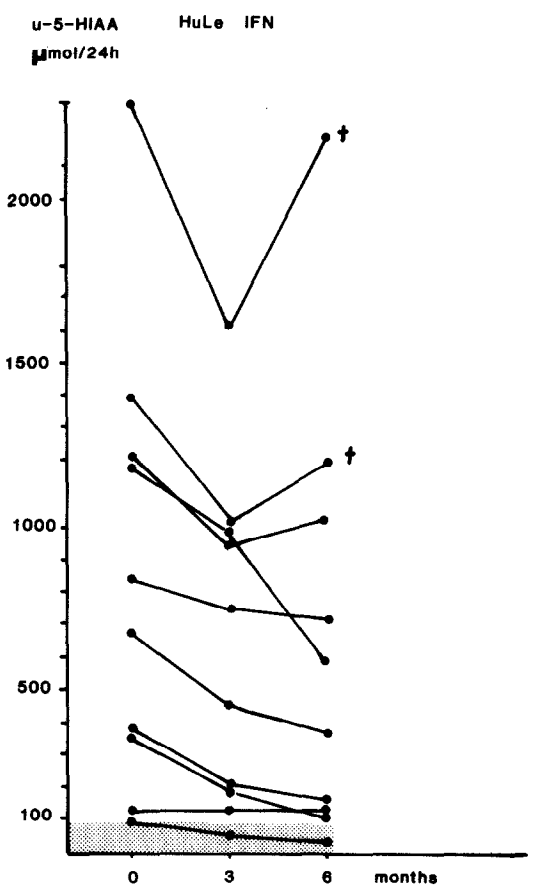

Fig. 2. *Effects of α-interferon on urinary* 5-*HIAA levels in* 10 *patients with malignant mid-gut carcinoid tumors.* (+) *indicates the death of the patient. Shaded area, reference range for urinary* 5-*HIAA* (<80 μmol/24 h).

A chi-square analysis of the proportions of patients with tumor responses, stable and progressive disease, performed between the two treatment arms, showed that interferon treatment at 6 months had a significantly higher proportion of responders and stable disease than chemotherapy ($P = 0.0039$).

At 12 months, a total of 18 patients had been treated with interferon and 11 patients with streptozicin plus 5-FU. Eight of the 18 patients (44%) receiving interferon showed an objective response, but none in the chemotherapy group ($n = 11$). No patient in the interferon group showed progressive disease, whereas six of 11 patients (54%) had tumor progression in the chemotherapy group. A similar comparison between the proportions of responders and stable disease in the chemotherapy and interferon groups at 12 months treatment showed $P = 0.0006$. A subjective response, i.e. less flushing and diarrhea, was noticed in 13 out of 18 patients receiving interferon (72%), and in only one (9%) of the patients on chemotherapy.

Side-effects of the treatment (*Table* 2)

The adverse reactions of chemotherapy were mainly severe vomiting 82% and impaired renal funtion with albuminuria (15%) and increased serum creatinine in 27% of the patients. 'Flu-like' symptoms for 3–5 days was the most frequent adverse reaction in patients receiving interferon, noted in 78% of the patients. A mild leukopenia (39%) and thrombocytopenia (22%) was also noticed.

Table 2. *Adverse reactions*

	IFN	S + 5-FU
Vomiting	0/18	9/11 (82%)
'Flu-like' symptoms	14/18 (78%)	0/11
Weight loss	2/18	0/11
Anemia	3/18 (17%)	1/11 (9%)
Leukopenia	7/18 (39%)	1/11 (9%)
Thrombocytopenia	4/18 (22%)	0/11
Albuminuria	2/18 (11%)	5/11 (45%)
Increased serum creatinine	0/18	3/11 (27%)
Increased liver enzymes	1/18 (6%)	1/11 (9%)
Increased serum triglycerides	2/18 (11%)	1/11 (9%)

DISCUSSION

Carcinoid tumors are slowly growing neuroendocrine tumors with a malignant potential. When metastases have appeared in the liver, the patient often presents the carcinoid syndrome with flush and diarrhea, which is closely related to hormone production by the tumor cells. If untreated, patients with the carcinoid syndrome have a median survival time of 2.5 years from diagnosis [3]. The ultimate treatment for patients with malignant carcinoid tumors has still to be elucidated. Chemotherapy is the most common treatment for these tumors. Streptozocin in combination with 5-FU is the only cytotoxic regime which has demonstrable effects. It has revealed an objective response rate of 33% in patients with metastatic carcinoid tumors [3]. However, other investigators, Junge *et al.* [11] and Schein *et al.* [1], did not see any tumor response, using the same treatment. In a similar study from our own group the response rate to streptozocin in combination with 5-FU was only 10% [4].

Treatment with interferon has, in the last few years, been tried in many types of tumors with antitumor effects on such malignant diseases as hairy cell leukemia [13], chronic myelogenous leukemia and non-Hodgkin's lymphomas [14, 15]. Interferon treatment has demonstrated objective tumor responses in 48% of the patients with mid-gut carcinoid tumors [5], and subjective improvement of flush and diarrhoea in 64%. In the present study, human leukocyte interferon was significantly better than chemotherapy with regard to antitumor responses and subjective improvement. Furthermore, patients initially treated with chemotherapy showed objective tumor responses after change to interferon.

Four patients died during the study, two in each arm of treatment. One in the chemotherapy group died from tumor progression and the other three (both in the interferon group) from cardiac heart failure. Interferon treatment could thus not prevent further development of cardiac failure. The progress of the already damaged heart valves with congestive heart disease could not be reversed. However, interferon treatment could decrease circulating hormone levels and arrest tumor growth for extended periods of time and improve the quality of life for the patients.

Recently, promising results of treatment with a new long-acting somatostatin analog, SMS 201-995, in patients with carcinoid syndrome have been published [16]. Although circulating hormone levels were reduced, no conclusive effect on tumor growth has been reported [17]. Combination therapy with this analog and α-interferons should be attempted in the future.

We thus think that interferon should be considered as a treatment alternative for patients with metastatic carcinoid disease. Both the objective and subjective tumor responses are superior to chemotherapy. Furthermore, the side-effects are less severe than with chemotherapy and the quality of life of patients is much improved.

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