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CYTOTOXIC TREATMENT IN PATIENTS WITH MALIGNANT CARCINOID TUMORS

Response to streptozocin—alone or in combination with 5-FU

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Abstract

Thirty-one patients with malignant carcinoid tumors were treated with streptozocin—alone (n=7) or in combination with FU (n=24). The responses to treatment were followed by the determination of tumor markers, urinary 5-HIAA, serum PP, HCG-α and -β subunits, as well as determination of the size of liver metastases on computerized tomography or ultrasonography. Three patients (9.7%) showed objective responses with a mean remission time of 2.7 months. Eighteen patients (58%) showed stable disease, whereas ten patients (32.3%) showed progressive disease directly from the start of therapy. A good correlation was found between the changes in tumor markers and tumor size, although the changes occurred earlier in the markers than in the size. Estimated median survival from the time of histologically verified carcinoid tumor was 41 months and from start of therapy 22 months. Our data indicate that combination treatment with streptozocin and 5-fluorouracil is of little value for patients with malignant carcinoid tumors.

Key words: Carcinoid, streptozin, 5-FU, carcinoid syndrome, 5-HIAA, HCG-α and -β, pancreatic polypeptide.

Streptozocin, a nitrosurea compound with antibiotic and antitumor activity, has for the last decennium been used with beneficial effects in the treatment of endocrine pancreatic tumors, especially insulinomas (7). Carcinoid tumors, which are closely related to endocrine pancreatic tumors, have also been treated with this agent. Varying results have been published (2, 4, 7, 8, 11). In the present study results of streptozocin treatment—alone or in combination with 5-FU—in 31 patients with metastatic carcinoid tumors are presented. The objective tumor responses are related to tumor size and/or tumor 'markers' (hormones).

Material and Methods

Thirty-one patients, 21 women and 10 men, with histologically verified carcinoid tumors, were investigated and treated with streptozocin, alone (n=7) or in combination with 5-fluorouracil (5-FU) (n=24). At the time of diagnosis the mean age was 54.7 years (range 21–82). The performance status was 1–2 (ECOG). The mean time from first symptoms of carcinoid tumor (flushing and/or diarrhea) until the initiation of cytotoxic treatment was 3.8 years (range 0.5–20).

In 25 of the patients, the primary tumors were located within the mid-gut region (ileum, jejunum, cecum). Three patients had bronchial carcinoid tumors, two had unknown primary tumor localization and one patient had a mediastinal carcinoid. Twenty-eight patients had metastases to the liver and/or skeleton and 24 of them presented the classical carcinoid syndrome, with both symptoms as flush or diarrhea and elevated level of urinary 5-hydroxyindoleacetic acid (5-HIAA). In 19 of the patients the primary tumors were resected. Tumor tissue specimens from all patients were histologically investigated, with the Grimelius (5), Sevier-Munger (12) and Masson (13) silver staining techniques. In all patients were the Grimelius silver staining positive indicating a neuroendocrine tumor and in 25 of the cases (80%), the Masson technique showed positive argentaffin reactions together with classical morphology of a mid-gut carcinoid tumor.

All patients were subjected to computerized tomo-

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graphy and ultrasonography of the abdomen. These investigations were performed prior to start of treatment and repeated every third month. Twenty-three patients (74%) underwent angiography of the celiac and superior mesenteric arteries to supplement the initial localization of the primary tumors and metastases.

Routine investigations of blood and urine were performed before start of treatment and prior to each treatment course. Liver and renal functions were checked, blood platelets and leucocytes were counted and the fasting blood sugar concentration was determined. The urinary 5-HIAA secretion was determined as an average of two 24-h urine samples, using the method of WAHLUND & EDLÉN (14). Serum pancreatic polypeptide (PP) and HCG-α and -β subunits were determined after an overnight fast, using earlier described radioimmunoassay techniques (6, 16). If 5-HIAA or peptide hormones were elevated by at least 50% above the reference range, they were used as tumor markers. Twenty-seven patients (87%) had at least one tumor marker to follow.

Streptozocin was obtained from the National Cancer Institute, Investigational Drug Branch, Bethesda, Md., USA. Vials of 1 g streptozocin was dissolved in 10 ml of saline just before every treatment course and administered intravenously as an induction therapy of 0.5 g/m^2 for 5 days. A maintenance therapy of 2 g was then given every third to fourth week. Seven cases are referred in the beginning of the study and got 1.5 g/m^2 as bolus injection once every third week. In the following 24 patients 5-FU was administered concurrently with the streptozocin at a dose of 400 mg/m^2. The mean duration of the streptozocin treatment was 7.5 months (range 3–20). The mean total dose of streptozocin was 12.4 g (range 9–30). The mean treatment period with 5-FU was 7.1 months (range 3–21), and the mean total dose of 5-FU was 8.3 g (1.5–33.2). Observation period is the same as treatment period.

Criteria for response. Objective tumor response was defined as a reduction of liver metastases by at least 50%, measured as the product of two perpendicular diameters on CT-scan and/or reduction of the principal tumor marker (5-HIAA) with 50% or more and no new tumor lesions developed during the observation period. *Stable disease* was defined as reduction of liver metastases by less than 50%, and/or reduction in the principal tumor marker (5-HIAA) by less than 50% and no new tumors developed. *Tumor progression* was defined as an increase in liver metastases by at least 25%, and/or increase of the principal tumor marker (5-HIAA) by at least 25% and/or appearance of new tumor lesions. The time of regression in patients with objective tumor response was defined as the time from start of treatment until first sign of tumor progression.

Statistical analyses. Mann-Whitney, Kruskal-Wallis and Sign tests were performed according to CONOVER (3).

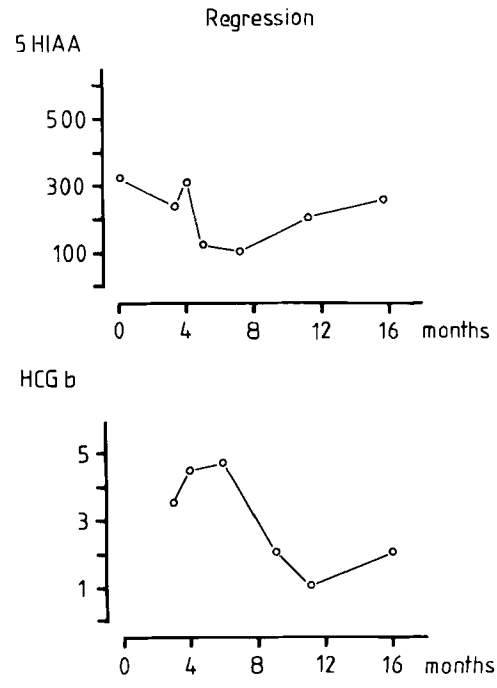

Fig. 1. Regression of tumor markers in a patient treated with streptozocin and 5-FU. Ref. values: 5-HIAA: <80 µmol/24 hours. HCG-α: Males and premenopausal females <3.0 µg/l, postmenopausal females <8.5 µg/l. HCG-β:<2.5/µg/l. PP: <0.4 ng/ml.

Results

Three of 31 patients (9.7%) showed objective tumor response. In all of them the response was seen in the tumor markers (Fig. 1). No patient showed significant reduction of tumor size. The mean time of response was 2.7 months (range 1–5), and all patients then subsequently relapsed. Two of the 3 patients with objective response were treated with the combination of streptozocin and 5-FU and one patient with only streptozocin. Eighteen patients (58%) showed stable disease. Twelve patients had stable disease for a mean period of 5.4 months (range 3–11) after start of treatment, but they all subsequently progressed. The other 6 patients remained stable for 5, 6, 7, 8, 9 and 18 months respectively after start of therapy. At this moment 4 of the patients received another form of treatment and 2 patients died, one of them in a heart attack and the other due to gut perforation and sepsis. The remaining 4 patients were given interferon treatment after the observation period.

Ten patients (32.3%) showed progressive disease immediately from start of therapy. Two of them progressed only in the tumor markers, but in 5 patients the liver metastases significantly increased (Fig. 2). Three patients progressed in both tumor markers and tumor size. Five of the patients with tumor progression were treated with the combination of streptozocin and 5-FU and 5 with only streptozocin.

Prior to start of therapy, 25 of the patients (80%) had

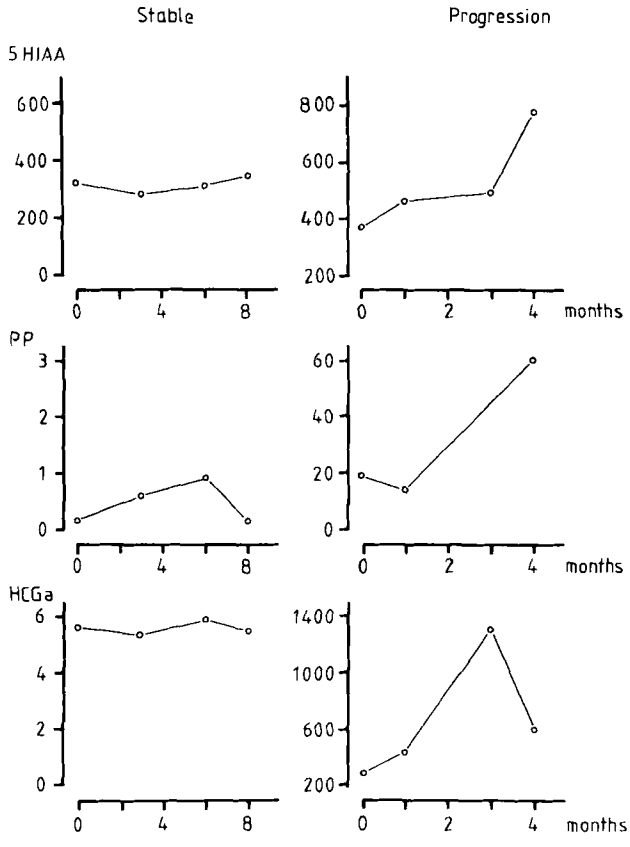

Fig. 2. Changes in tumor marker concentrations in one patient with stable disease and in another with progressive disease, both treated with streptozocin and 5-FU. Ref. values according to Fig. 1.

elevated urinary 5-HIAA levels, median 366 μmol/24 h (range 26–1926). Serum HCG-α and -β were measured in 25 of the patients. Eight of them (32%) had elevated HCG-α and 3 (12%) HCG-β. Ten of 26 patients (38%) had elevated levels of PP.

Totally 25 of the 31 patients showed sooner or later a progression of their diseases. In 16 of them (64%) increasing levels of 5-HIAA were the first sign of tumor progression. Radiographic changes followed later in 7 patients after a mean time of 3 months (range 1–5). However, in 5 of 25 patients (20%), developement of new metastases was the first sign of tumor progression and in 4 patients (16%) the tumor markers rose parallel with the development of new metastases. No patient showed declining tumor markers and a simultaneous increase of the tumor size on CT-scan or ultrasound (Figs 1, 2).

Thirteen of the 31 patients (42%) died within the observation period. The estimated median survival time from start of therapy to death or onset of other treatment was 22 months. The estimated median survival time from histological diagnosis of carcinoid tumor was 41 months. The 5-year mortality rate was 52%. The estimated median survival time from the start of definitive symptoms of flush and/or diarrhea was 9 years, and the 5-year mortality rate was 22%.

Table

Toxicity associated with streptozocin therapy in 31 patients

Therapy	No.	Percentage
Hematologic		
a) WBC<3 500/mm³	2	6.4
b) Platelets<100 000/mm³	0	
Sustained hyperglycemia		
Fasting blood glucose >5.7 mmol/l	2	6.4
Renal		
a) Albuminuria >30 mg/24 hours	13	42
b) Creatinine clearance reduced F<75 ml/min, M<80 ml/min	8	26
c) Serum creatinine > 106 μmol/l	3	9.7
Liver		
a) ASAT > 0.6 ukat/l	3	9.7
b) ALAT > 0.6 ukat/l	3	9.7
c) Bilirubin > 21 μmol/l	1	3
d) Alcaline phosphatase >4 μmol/l	3	9.7
e) Lactate dehydrogenase > 6.7 ukat/l	0	
Nausea and vomiting	28	90
Others		
a) Myocardial infarction	1	
b) Venous thrombosis	1	
c) Diarrhea	1	
d) Pain in the liver region	1	
e) Menorrhagia	1	

The 7 patients treated with streptozocin alone are all dead with a mean survival time of 7.5 months. In the patients treated with combination therapy of streptozocin and 5-FU, 9 of 24 are dead. The mean survival time for these 9 patients was 18 months which was significantly longer ($p<0.05$) than for the patients treated with only streptozocin.

The patients who progressed directly from start of treatment were significantly ($p<0.05$) younger than the rest of the patients. No significant difference between responders and nonresponders regarding pretreatment levels of 5-HIAA was found. Nor did the duration of the disease prior to treatment seem to interfere.

Six out of 25 patients (24%) with mid-gut carcinoid tumors progressed directly from the start of treatment. The remaining patients with mid-gut carcinoids showed stable disease (16/25) or regression (3/25). Both patients with unknown primary tumors as well as one with a bronchial carcinoid and the one with mediastinal carcinoid tumor progressed directly from the start of treatment.

Impaired renal function was the most common treatment limiting side effect of the therapy (Table). Reversible albuminuria and reduced creatinine clearance were seen in 6 out of 31 patients (19%), and in two cases the treatment was stopped because of developing uremia. Hematologic side effects were infrequent in the study (6%).

Sustained hyperglycemia was found in only 2 patients (6%). Liver toxic effects were reversible and transient increase in ASAT, ALAT and alkaline phosphatases were seen in only 2 patients. Subjective symptoms as nausea and vomiting were found in 90% of the patients, in spite of prophylactic treatment with metoclopramide, antihistamines and anticholinergic. Other complications, such as diarrhea, abdominal pain, deep vein thrombosis and profuse menstrual bleeding were noted in exceptional cases. One patient developed myocardial infarction during a treatment period.

Discussion

The ultimate treatment of malignant carcinoid tumors has not yet been found. Different combinations of chemotherapy has been tried for the past 20 years and the combination of drugs which has proven some substantial value so far, is the combination of streptozocin and 5-fluorouracil. However, in different studies the reported response rates are very varying (2, 4, 7, 8, 11). MOERTEL & HANLEY (8) treated 42 patients with a combination of streptozocin and 5-fluorouracil and reported an objective response rate of 33%. A similar result was also reported by CHERNICOFF et coll. (2) with an objective response observed in 2 of 10 carcinoid patients treated with the same combination of drugs. However, JUNGE et coll. (7) as well as SCHEIN et coll. (11) did not find any objective responses with the same combination of chemotherapy. Our result with an objective response rate of 9%, lasting only for 2.5 months, is dismal and more in agreement with the last 2 papers.

The divergent results might have several explanations, such as differences in patient selection and the criteria for objective responses. In their study MOERTEL & HANLEY (8) could demonstrate a higher response rate, 33% versus 24%, if the patients had carcinoid syndrome or not. This might indicate a heterogeneity among carcinoid tumors with different responses to treatment. Although we present lower objective response rates we have a longer median survival time (22 months) compared with 11.2 months in the study of MOERTEL & HANLEY. Another difference between our study and theirs is the criteria of objective tumor responses. All our patients have been investigated by CT-scan and/or ultrasound to measure the tumor size, whereas in the ECOG study several centers were involved and the investigators measured the liver edge below the right costal margin. If the patient has a carcinoid heart disease with liver enlargement, treatment of heart decompensation will result in shrinking liver size without reduction of tumor size. The determination of tumor markers is an important adjunct in the evaluation of objective responses in carcinoid patients. All of our responders showed a more than 50% decrease in the plasma concentration of tumor markers or urinary levels of 5-HIAA, whereas no significant decline was noted in tumor size. Twenty-five of 31 patients showed a progression of their carcinoid disease, despite of streptozocin treatment and the first sign of tumor progression was seen in tumor markers in 64% of the patients.

Chemotherapy including a combination of streptozocin plus 5-fluorouracil seems not to be of any substantial value for our patients with malignant carcinoid tumors. At the moment more promising therapeutic alternatives have been published, such as interferon treatment (9, 10), hepatic artery ligature (1) and very recently treatment with the somatostatin analogue SMS 201-995. Besides, significantly higher objective response rates, the side effects of these treatments, are less severe than streptozocin treatment.

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