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TREATMENT OF CARCINOID SYNDROME WITH RECOMBINANT INTERFERON ALPHA-2a

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The prognosis and the quality of life of patients with carcinoid tumors is related either to symptoms from the substances secreted or to progressive tumor growth. Medical treatment with cytotoxic agents is of marginal value for increasing life expectancy and reducing clinical symptoms. Recent studies with interferon have shown interesting results. In the present investigation, 22 patients with carcinoid tumors and syndrome were treated with recombinant interferon alpha-2a (r-IFN alpha-2a) at the dose of 6×10^6 IU intramuscularly daily for 8 weeks and three times weekly thereafter. The primary tumor was localized in the foregut (n = 11), midgut (n = 7), hindgut (n = 1), and unknown site (n = 3). Most cases had liver metastasis. Seventeen patients had elevated 5-hydroxyindoloacetic acid (5-HIAA) excretion and 5 had flushing and/or diarrhea as the only clinical manifestation. Six cases presented a complete syndrome (flushing, diarrhea and 5-HIAA excretion). Control of symptoms was obtained in 80% and a 5-HIAA level reduction in 58% of the patients. The interferon treatment was more effective for control of the carcinoid syndrome than for control of tumor growth. The treatment was well tolerated and fever, myalgia, anorexia and fatigue were the most frequent side-effects.

Carcinoids represent the most frequent subtype of neuroendocrine tumors (1, 2). The prognosis is related to tumor growth rate and the presence of symptoms caused by secreted substances. The carcinoid syndrome is characterized by flushing, diarrhea and, more rarely, by valvular heart disease. The primary site of the tumor is an important factor for the development of the syndrome. Foregut and midgut carcinoids are thus frequently associated with this disorder, which is rarely associated with tumors of hindgut origin (3). The physiopathologic mechanism of the syndrome has not been fully defined. However, increased serotonin production has been associated with high levels of a few other vasoactive peptides and, just as serotonin might be responsible for the diarrhea, kallicrein, bradykinin and tachykinin might induce flushing. The secretion of prostaglandins and histamin has also been associated with carcinoid tumors (4, 5). Increased urinary excretion of the serotonin metabolite, 5-hydroxyindoloacetic acid (5-HIAA), is clearly the most reliable laboratory confirmation of an actively secreting tumor.

In the early stage, surgical removal of the tumor is often curative. However, in the presence of carcinoid syndrome, curative surgery is not possible since clinical symptoms indicate widespread metastases. Consequently, treatment has two goals: to inhibit tumoral growth and to control symptoms. The results obtained with cytotoxic chemotherapy are disappointing, with response rates of 20% and partial responses of short duration (6–8). The drugs used to control symptoms due to released substances include a wide variety of antidiarrheal agents, adrenergic blocking agents, kinin antagonists, serotonin antagonists and corticosteroids. However, none of these is capable of obtaining complete palliation by itself.

The first data reported by Öberg et al. (9, 10) on the activity of natural human leukocyte interferon (*IFN*) *in*

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patients with malignant carcinoids and carcinoid syndrome were encouraging. Although the mechanism of the action of IFN on carcinoid tumors has yet to be elucidated, some studies support the hypothesis of a direct inhibitory effect on hormone synthesis and tumor cell proliferation. The availablility of recombinant IFN (r-IFN), and the expected good tolerance to low-doses of r-IFN alpha, led us to undertake this study, aimed at evaluating the efficacy of this agent in the control of carcinoid syndrome (11).

Material and Methods

The study was conducted by the Italian Trials in Medical Oncology (I.T.M.O.) Group. The Division of Medical Oncology B of Milan's Istituto Nazionale Tumori was the coordinating center, and the Division of Pathology of the Istituto Nazionale Tumori was the reference center for central pathology review.

The inclusion criteria were a histologically confirmed diagnosis of carcinoid tumor, elevated 5-HIAA urinary excretion, and/or the presence of disease-related symptoms, age < 78 years and a performance status ≤ 2 (ECOG scale). The included patients could have been previously treated with surgery, limited field radiotherapy and at most one chemotherapy regimen. Normal renal, hepatic and haematological functions were required. The exclusion criteria were previous treatment with biological response modifiers, the presence of severe concomitant diseases (in particular active heart disease), and a life expectancy of less then 3 months with rapidly progressive life-threatening metastases. The nature of the protocol was explained to each patient and their informed consent obtained. The staging procedures, including physical examination, ECG, blood biochemistry, chest x-ray, and abdominal ultrasound/computed tomographic scan (CT) were performed before treatment and every two months thereafter.

The level of 5-HIAA was evaluated by means of high performance liquid chromatography as the average of two 24 h urine collections, taken before, and every two months after starting treatment.

Recombinant IFN alpha-2a (Roferon-A, Hoffman La Roche, Milan) was given intramuscularly at 3×10^6 IU daily for the first 3 days; the dose was then increased to 6×10^6 IU daily until the end of the eighth week, and three times per week thereafter. Therapy was continued for 12 months or until objective progression. The drug was self-administered in an out-patients setting, and the patients were carefully monitored to verify that they were taking it regularly.

Toxicity was classified according to WHO criteria (12) and dose reduction or treatment interruption was allowed in the case of persistent severe toxicity. Acetominofene was routinely used for palliation of fever and myalgia.

Flushing and diarrhea were checked monthly, and any reduction in the intensity of clinical symptoms was assessed by the patients themselves as being complete, or more or less than 50% of the baseline intensity. The daily number of flushing and/or diarrhea attacks was recorded. Three types of response were evaluated: biochemical, symptomatic and tumoral. For 'biochemical response', complete remission (CR) was defined as the return of 5-HIAA urinary excretion values to the normal range for at least one month, and partial response (PR) as $> 50\%$ decrease for at least one month. For 'symptomatic response', CR was defined as complete relief from all symptoms, and PR as reduction by at least 50% of both frequency and intensity of flushing and/or diarrhea. 'Tumor response' was defined according to the WHO criteria (12).

Results

Between August 1989 and December 1991, 22 patients with metastatic carcinoids, and elevated 5-HIAA excretion and/or symptoms of carcinoid syndrome were treated. Their main characteristics are summarized in Table 1. Of the 7 patients with midgut carcinoids, 6 had primary tumor in the ileum, while the seventh had cecal carcinoid. Liver metastases were present in 19 patients. Seventeen of the 22 cases had elevated 5-HIAA levels with a median baseline value of 45 mg/24 h (range 12–243). Five patients with normal 5-HIAA level had flushing or diarrhea as the only clinical manifestation. Six patients presented complete carcinoid syndrome including flushing, diarrhea and abnormal 5-HIAA levels. All but one patient had undergone palliative resection, and 6 cases had received chemotherapy without any significant benefit.

The median duration of IFN treatment was 10 months (range 2–12); therapeutic response is shown in Table 2. All six patients who presented a complete syndrome with elevated 5-HIAA excretion, flushing and diarrhea, obtained subjective symptom relief, and 4 of them achieved a reduction of the 5-HIAA level by 50% or more. In one case, all three manifestations completely disappeared. A 'symptomatic response' was obtained in 8 patients with flushing (80%) and in 9 with diarrhea (90%). These re-

Table 1

Main patient characteristics

Eligible	22
Males/Females	9/13
Median age (range)	56 (39–77)
PS (ECOG scale): 0/1	13/9
Primary site:	
foregut	11
midgut	7
hindgut	1
unknown	3
Elevated 5-HIAA	17
Normal 5-HIAA	5
Carcinoid syndrome	6

Table 2

Therapeutic results

Features	No. Eligible	Response		
		CR	CR + PR	%
Elevated 5-HIAA	17	6	10	58
Flushing	10	5	8	80
Diarrhea	10	4	9	90
Carcinoid syndrome	6	1	6	100

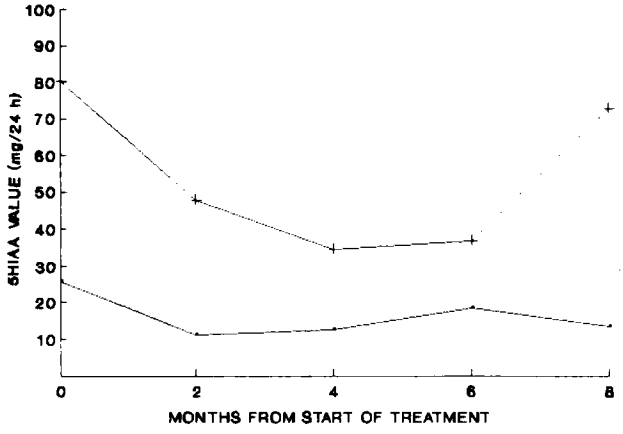

Figure. 5-HIAA levels in patients with partial response (+ , n = 4), and in patients with stable or progressive disease (0, n = 6).

sponses occurred after one month, and lasted throughout the period of treatment. 'Biochemical remission' was observed in 10 patients within the first two months of treatment and had a median duration of 4 months. Among the patients with 'biochemical response', two different patterns in the reduction of 5-HIAA levels were observed in relation to the behavior of the tumor (Figure). As regards 'tumor response', four patients showed partial objective regression, while stable disease was observed in 8 cases. Three of the 4 objectively responding patients also had a complete return to normal 5-HIAA values; the fourth had a more than 50% reduction. A transitory normalization of 5-HIAA levels was observed in one patient with progressive disease (Table 3).

Side-effects are summarized in Table 4. The most frequent side-effects, observed at the start of IFN treatment

Table 3

Relationship between objective tumor response and 'biochemical response'

Tumor evaluation	No. of patients	Biochemical response			
		CR	CR + PR	SD	DP
Partial responses	4	3	4	–	–
Stable disease	8	2	5	3	–
Disease progression	5	1	1	2	2

Table 4

Side effects related to interferon treatment in 22 patients

	WHO grade			Total
	1	2	3	
Fever	3	3	2	8
Chills	2	2	1	5
Myalgia	5	4	3	12
Leukopenia	2	4	2	8
Anorexia	2	6	2	10
Nausea	1	1	–	2
Fatigue	2	5	3	10
Headache	1	2	1	4

in about 54% of the patients, were myalgia, fatigue, anorexia and fever. The fever, which rarely exceeded 39°C, as well as myalgia and fatigue, was of short duration. One patient experienced a grade 3 flu-like syndrome, and IFN treatment was continued at 75% of the initial dose.

Discussion

The mechanisms responsible for the carcinoid syndrome are incompletely known, which at least partly, explains the lack of a clear definition of effective treatment approaches. Generally, the frequency and severity of symptoms are related to the serotonin production which is reflected in urine 5-HIAA excretion. Some cases, however, with the syndrome have minimal 5-HIAA excretion, and some patients with a marked elevation of urinary 5-HIAA values show no signs of the syndrome. Symptoms are present when the tumor products have direct access to the systemic circulation without preceding hepatic detoxification. This usually occurs in the presence of liver metastasis. All our patients with flushing and diarrhea, but with normal 5-HIAA excretion levels, had liver metastasis.

In relation to the various possible mechanisms of action, many pharmacological methods have been investigated. The published results, however, often concern clinical experiences of very small numbers of patients, and sometimes the recommendations are made based on the outcome of one single case only (13–15). The therapeutic effect has often been poorly defined, and none of these agents can reliably and effectively palliate all symptoms of the syndrome.

Previous studies with natural leukocyte IFN alpha have reported a biochemical response rate of 47% and control of symptoms in 64% of cases (9, 10). However, recently Ahren et al. (16) reported that they were unable to reproduce these positive results. Moertel et al. (17), using a higher dose of r-IFN alpha-2a (24×10^6 IU) concluded that the potential value of the drug was outweighed by its adverse effects. Also some studies have shown disappointing results (18–21). In our own investigation, however,

r-IFN alpha-2a induced a 'biochemical response' in 58%, with complete relief of symptoms in about 50% of the patients. It is noteworthy that 62% of cases with stable disease obtained a reduction of the 5-HIAA level. Our general impression was that the 'biochemical response' as a rule was more pronounced than the 'tumor response' which might be explained by a direct interaction of r-IFN with hormonal secretion. Given our small number of patients and the slowly growing tumor, however, no certain conclusions can be drawn concerning the possible influence of r-IFN on the tumor growth.

The treatment was well tolerated for one year without any severe side-effects; we therefore believe that the schedule we used can be administered for a longer time period. All 'biochemical remissions' occurred during the first 8 weeks of treatment. It thus seems as a correct way to use r-IFN in carcinoids to treat patients with a high dose for the first 2 months and then, for responding patients, to continue at a lower dose. The treatment should be stopped if no effect is seen during the first 2-month period.

The observation of an antisecretory activity of r-IFN alpha-2a suggests that this agent may be a useful alternative to the medical management of carcinoid syndrome in patients suffering from slowly growing carcinoids. In case of progressive disease, it might be of value to combine r-IFN therapy with conventional cytotoxic chemotherapy to produce additive and synergistic effects.

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