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Treatment of Metastatic Carcinoids and Other Neuroendocrine Tumors with Recombinant Interferon-Alpha-2a

A Study by the Italian Trials in Medical Oncology Group

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Background. **Using a wide range of interferon (IFN) doses and schedules, a number of authors have found them to be active against neuroendocrine tumors.**

Methods. **To verify the clinical activity of IFN, 49 evaluable patients with advanced stage low- and intermediate-grade neuroendocrine tumors were treated with recombinant IFN-alpha-2a at a daily dose of 6×10^6 IU intramuscularly for 8 weeks, and 3 times weekly thereafter. The predominant histotype was carcinoid, although a few cases had malignant islet cell tumors, medullary thyroid carcinoma, Merkel cell carcinoma, or other neuroendocrine tumors. All of the patients had measurable lesions and most had multiple sites. Carcinoid syndrome was present in 14 cases.**

Results. **After a median treatment duration of 6 months, complete regression was achieved in 1 of the 7 cases of medullary thyroid carcinoma, and partial response was observed in 4 of 34 carcinoids. Response duration ranged from 1–11 months. Control of the syndrome was obtained in nine patients and a greater than or equal to 50% reduction of 5-hydroxyindoleacetic acid in eight patients. The treatment was well-tolerated. The most frequently observed side effects were fever, flu-like syndrome, and leukopenia. After 12 months of recombinant IFN-alpha-2a, 15 cases in progression and 4 with stable disease or partial response received another treatment (either radiometabolic therapy with I^{131} metaiodobenzylguanidine or polychemotherapy with streptozotocin plus epirubicin).**

Conclusions. **The use of recombinant IFN-alpha-2a at these doses is well-tolerated and effective in controlling carcinoid syndrome (complete remission plus partial remission, 64%), although it has limited activity on tumor growth inhibition. No definitive data can be given for the other protocol treatments. *Cancer* 1993; 72: 3099–105.**

Key words: carcinoid tumor, neurosecretory system, interferon-alpha-2a, biologic tumor markers.

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Neuroendocrine neoplasms make up a large, heterogeneous spectrum of lesions whose common denominator is a histopathologic "organoid" growth pattern, the argyrophilia of the cells, the immunocytochemical detection of endocrine markers, and the ultrastructural evidence of secretory granules. Their heterogeneity is a result of differences in their histogenesis, structure, functional activity, and clinical behavior. Carcinoid tumors are the most frequent neuroendocrine neoplasms and account for 0.05–2.0% of all tumors.[1,2] According to the World Health Organization classification,[3] the term carcinoid refers to tumors of the diffuse endocrine system, excluding those of the pancreatic islets and medullary thyroid carcinomas (MTC). In Italy, the incidence of carcinoid tumors accounts for 13% of all small bowel tumors.[4] Clinical outcome is related to tumor progression and the symptoms induced by some substances secreted by the tumor itself. Tumor progression often leads to the onset of liver metastasis, lymph nodes and lung being other frequent sites of involvement. It is the release of serotonin, tachykinin, and bradykinin from the neoplasm that causes the carcinoid syndrome, and 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA), the metabolite of serotonin, is an appropriate marker for following the effectiveness of treatment or disease progression.

Surgery is the treatment of choice for local disease, but systemic therapy is required during the progressive metastatic phase or in the presence of uncontrolled hormonal symptoms. The goal of medical treatment is to inhibit tumor growth and control the clinical symptoms due to hormonal secretion. The results of chemotherapy studies are discordant. Moertel[5] reported a response rate of 26% when fluorouracil was used in cases of malignant carcinoid tumors. Streptozotocin (STZ) alone has been shown to be active against islet cell carcinoma,[6] although polychemotherapy is responsible for the highest response rates.[7,8] In carcinoid tumors, no clear advantage for the use of combined drugs has been documented.[9–11]

In an attempt to improve both tumor control and symptom relief, other treatment approaches using noncytotoxic agents, such as interferons (IFN), have been adopted. Although the antineoplastic mechanisms of IFN are not fully known, alpha-interferon has been shown to have inhibitory effects on oncogene expression, DNA replication, and protein synthesis. Tumor cell division is mainly blocked in the G_0-G_1 phase, but a definite cytotoxic effect has not yet been demonstrated; control could also be indirect and occur through the activation of the immunoregulatory system.[12,13]

On the basis of these biologic data, various authors have already investigated the clinical activity of a wide range of different doses and schedules of IFN in neuroendocrine tumors.[14–16] Given that no definitive conclusions have yet been drawn as far as the antitumor activity and proper dose of IFN are concerned, it was decided to test the activity of recombinant IFN-alpha-2a (rIFN-alpha-2a) using an original schedule administered for a maximum of 12 months.

Patients and Methods

Patients

The 53 patients entering this ITMO Group study came from 23 different centers, coordinated by the Division of Medical Oncology B, Istituto Nazionale Tumori, Milan, Italy. To be included, the patients had to have histologic diagnosis of carcinoid or other neuroendocrine tumor with progressive metastatic disease. In cases of histologic uncertainty, the Division of Pathology, Istituto Nazionale Tumori, undertook pathologic reviews. In all cases, diagnosis was based on the examination of tissues routinely fixed on hematoxylin and eosin stained slides without immunocytochemical phenotyping. Pretreatment with surgery and/or limited radiation therapy fields was allowed, as was any previous chemotherapy discontinued for more than 1 month (excluding STZ and anthracyclines). None of the patients had previously received any biologic response modifiers, and all of them had to be younger than or equal to 78 years of age and have a performance status less than or equal to two (Eastern Cooperative Oncology Group scale). Adequate renal (serum creatinine < 1.5 mg/dl), hepatic (bilirubin < 3 mg/dl), and hematologic functions (white blood count $\geq 4000/mm^3$ and platelet count $\geq 120{,}000/mm^3$) were also required, and at least one lesion had to be measurable. The exclusion criteria were the presence of severe concomitant illness, active heart disease, and a life expectancy of less than 3 months with rapidly progressive life-threatening metastases.

The nature of the program was explained to each patient, and informed consent was obtained according to the standard procedures followed by each of the participating institutions. The staging procedures performed before starting therapy included physical examination, a biochemical profile, chest X-ray, electrocardiogram, and abdominal ultrasound/computed tomography scan; additional procedures (percutaneous liver biopsy, laparoscopy, gastrointestinal series) were used according to each clinical presentation.

Tumor Marker Analysis

The level of 5-HIAA was evaluated by means of high-performance liquid chromatography of a 24-hour urine sample. Calcitonin, human chorionic gonadotropin

beta subunit, and neuron-specific enolase (NSE) serum levels were determined by radioimmunoassay. Serum samples, drawn immediately before the start of treatment and every 2 months thereafter, were collected in ordinary plastic tubes, frozen, and stored at −20°C.

Treatment

Patients received rIFN-alpha-2a (Roferon-A, Hoffman La Roche Basel, Switzerland) at a daily dose of 3×10^6 IU for the first 3 days. The dose was then increased to 6×10^6 IU, administered daily for the first 8 weeks and three times per week thereafter. The rIFN-alpha-2a was given intramuscularly into one of the gluteus muscles. Patients were admitted to the hospital for the beginning of treatment; the drug was then self-administered in an outpatient setting, the patients being carefully monitored to ensure they took it regularly. At the time of every response evaluation, the physician questioned the patient directly and, during physical examination, special care was taken to investigate injection sites. Allowance was made for dosage reduction or treatment interruption in the event of persistent or severe toxicity, classified according to World Health Organization grading. Acetaminophen was routinely used for palliation of fever and myalgia. Therapy continued until objective tumor progression or for a period of 12 months. In the presence of persistent disease, patients received a different treatment. Radiometabolic therapy with I^{131} metaiodobenzyl-guanidine was activated in cases where an intensive scan uptake correlated with disease extension. In other cases, polychemotherapy with STZ (500 mg/m^2 intravenously on days 1, 2, and 3) plus epirubicin (75 mg/m^2 intravenously on day 1) was administered. The cycles were repeated every 3 weeks.

Evaluation of Response

History, physical examination, hemogram, blood biochemistry, and tumor measurement by ultrasound/computed tomography and radiograph were performed every 2 months. Flushing and diarrhea were checked monthly. The intensity of clinical symptoms was assessed by means of a three-grade scale (mild, moderate, and severe), and the number of flushing and/or diarrhea attacks was recorded. Three categories of response were assessed: (1) tumor, (2) biochemical, and (3) symptomatic. Tumor response was defined according to International Union Against Cancer criteria: complete remission (CR), defined as complete disappearance of all known disease for a minimum of 1 month; partial remission (PR), defined as greater than or equal to 50% decrease in the sum of the products of the two largest perpendicular diameters of all tumor masses for at least 1 month; stable disease, defined as less than 50% decrease or less than 25% increase in the size of measurable lesions; and progressive disease, defined as greater than or equal to 25% increase in any tumor lesion or the appearance of new sites. For biochemical response, CR was defined as the return of the elevated tumor markers to within the normal range for at least 1 month, and PR was defined as greater than or equal to 50% decrease for at least 1 month. For symptomatic response, CR was defined as the complete relief of all symptoms, and PR was defined as a reduction of at least 50% in both the frequency and intensity of flushing and/or diarrhea attacks.

Table 1. Patient Characteristics

Characteristic	No. of patients
Evaluable	49
M/F	24/25
Age (yr)	
Median	60
Range	39–77
Performance status 0–1	49
Carcinoid syndrome	14
Flushing	4
Diarrhea	4
Flushing and diarrhea	6
Abnormal urinary 5-hydroxyindoleacetic acid excretion	15
Histologic type	
Carcinoid	34
Malignant islet cell tumors	4
Medullary thyroid carcinoma	7
Merkel cell carcinoma	2
Well-differentiated neuroendocrine carcinoma of the lung	1
Neuroendocrine carcinoma of the breast	1

Results

Between August 1989 and December 1991, 53 eligible patients were sequentially enrolled in this multicenter trial; 49 were evaluable for response. Of the four non-evaluable patients, there was a lack of adequate information for three and one dropped out for severe toxicity (fatigue and leukopenia) within the first month. The main characteristics of the evaluable patients are listed in Table 1. The predominant histologic type was carcinoid (diagnosed in 34 patients). The primary sites of the 19 foregut carcinoids were: pancreas (n = 10), bronchus (n = 5), stomach (n = 3), and thymus (n = 1). Five patients affected by pancreatic carcinoids had abnormal 5-HIAA excretion. In addition, there were four islet cell tumors (three insulinomas and one glucagonoma), seven medullary carcinomas of the thyroid gland, two

Table 2. Characteristics of Patients Who Responded to Treatment

Age (yr)	Histologic type	Primary site	Disease extension	Objective response	Time to response (mo)	Response duration (mo)
63	Medullary	Thyroid	Mediastinal nodes	Complete	4	11
56	Carcinoid	Lung	Lung, abdominal nodes	Partial	11	1
54	Carcinoid	Midgut	Liver, abdominal nodes	Partial	4	10
39	Carcinoid	Foregut	Lung, pancreas, liver	Partial	10	5+
72	Carcinoid	Midgut	Liver, ileum, abdominal nodes	Partial	2	2

neuroendocrine (Merkel cell) carcinomas of the skin,[17] one well-differentiated neuroendocrine carcinoma of the lung,[18] and one neuroendocrine carcinoma of the breast.[19] Thirty-six patients had multiple sites and 4 had bulky disease (defined as a mass diameter of 10 cm or greater). The most frequent site of metastasis was the liver. Abnormal 5-HIAA urinary excretion was present in 15 patients (median, 21.8 mg/24 h; range, 11.5–243.0), carcinoid syndrome in 14 patients, and both in 7 patients. Regarding previous treatments, 20 patients had been treated with radical surgery and 6 had received palliative resection. Cytotoxic drugs, including fluorouracil and cisplatin (CDDP), had been administered in 11 cases. Fourteen patients had not received any previous therapy, and 7 had been given more than 1 treatment. After a median treatment duration of 6 months (range, 2–12), five patients (10%) showed an objective response. Stable disease was documented in 16 patients, 9 of whom received rIFN-alpha-2a for 12 months. Progressive disease was observed in 28 patients. The main characteristics of the responders are listed in Table 2. In particular, one patient affected by MTC with 3-cm diameter mediastinal nodes assessed by computed tomography scan experienced a CR. It is noteworthy that a long period of treatment was required before obtaining a response in two patients. The responding patient with a lung carcinoid obtained PR after 11 months of treatment and, in accordance with the protocol, received chemotherapy 1 month later. None of the responders had been pretreated with chemotherapy.

Our results of carcinoid syndrome are listed in Table 3. Nine patients (64%) had a symptomatic response, with the complete disappearance of symptoms for a median duration of 5 months in five patients. In all patients, the response was obtained within the first 2 months of treatment. The 5-HIAA levels in the eight patients with biochemical response are shown in Figure 1. The reduction generally occurred after 8 weeks of treatment, with a median duration of 4 months. In three of the four patients with carcinoids who had an objective response, their 5-HIAA levels also returned to normal; the remaining patient showed a reduction of more than 50%. There was also a concomitant biochemical response in four patients who experienced subjective relief of symptoms. Six patients had abnormal NSE values, but we have no further data to assess their behavior during the treatment. No abnormal baseline human chorionic gonadotropin beta subunit values were found in any of our patients. All of the seven patients affected by MTC had high-baseline calcitonin values. No reduction in the tumor marker was observed, not even in the patient with a clinically documented objective CR.

Side effects were analyzed according to World Health Organization grade and are listed in Table 4. The most frequent side effects observed in about 65% of patients during IFN treatment were fever, myalgia, and fatigue. The fever, which rarely exceeded 39°C, as well as the myalgia and fatigue were short-lasting. Chills, nausea, and headache were less frequent. In five patients, the treatment was administered at lower dosages. Four patients experienced grade 3 flu-like syndrome, and treatment was continued at 75% of the initial dose in one patient and 50% in three patients. Grade 3 liver toxicity requiring a 25% dose reduction was documented in one patient. No patient died of toxicity.

Nineteen patients in progression or with persistent disease after 12 months of rIFN-alpha-2a received another treatment. A polychemotherapeutic schedule with STZ plus epirubicin was administered in 15 patients, 1 of them experiencing a PR lasting 5 months. Four patients were treated with I^{131} metaiodobenzylguanidine therapy, three being evaluable because one is still on treatment. In one patient, a PR lasting 5 months was reported. The results of the treatment programs are listed in Table 5. No severe side effects were observed during either the polychemotherapy or radiometabolic treatment.

Discussion

The medical treatment of neuroendocrine tumors is still questionable. The control of tumor growth and a reduction in the clinical symptoms due to hormonal secretion by the tumor itself are the main objectives for clinicians.

Table 3. Results of Carcinoid Syndrome

Features	No. of eligible patients	Response		
		Complete	*Complete + partial*	*Percent*
Carcinoid syndrome	14	5	9	64
Flushing	10	5	7	70
Diarrhea	10	3	7	70
Abnormal urinary 5-hydroxyindoleacetic acid	15	6	8	53

* Median baseline value: 21.8 mg/24 h (range, 11.5–243).

Reports on the use of active antineoplastic drugs in such tumors regard fluorouracil, doxorubicin, dacarbazine, STZ, and CDDP.[20,21] However, chemotherapy is of marginal value in reducing clinical symptoms and obtaining objective responses. The use of rIFN has been tried in many types of tumors and has been shown to possess some therapeutic effects on neuroendocrine tumors with distant spread.[22]

The activity of natural human leukocyte IFN was documented by the Swedish study,[23] which, when using IFN at a dose of 3–6 $\times$ 10^6 IU three times a week, obtained objective tumor regressions in 11% of patients and biochemical responses in 53%.

In an attempt to reduce the side effects associated with human leukocyte IFN, Smith et al.[16] tested the activity of rIFN-alpha at a dose of 10 $\times$ 10^6 IU/m^2. No objective tumor regressions were observed, but 36% of the patients had a reduction of at least 50% in 5-HIAA excretion, and 67% achieved symptomatic relief of carcinoid syndrome. The treatment was well tolerated.

High-dose rIFN-alpha-2a (i.e., 24 $\times$ 10^6 IU intramuscularly three times a week) induced more objective regressions.[15] However, the responses only persisted for a median of 7 weeks. Because of the side effects encountered, the schedule was not recommended for the routine treatment of carcinoid tumor or syndrome.

With the aim of achieving significant tumor response rates with fewer side effects than those previously encountered, we treated 53 patients affected by neuroendocrine tumors with rIFN-alpha-2a at a daily dose of 6 $\times$ 10^6 IU for the first 8 weeks, reduced to 3 times per week thereafter. We included one patient with well-differentiated neuroendocrine carcinoma of the lung, which is characterized by a biologic behavior falling somewhere between that of a carcinoid and small-cell carcinoma, thus underlining the heterogene-

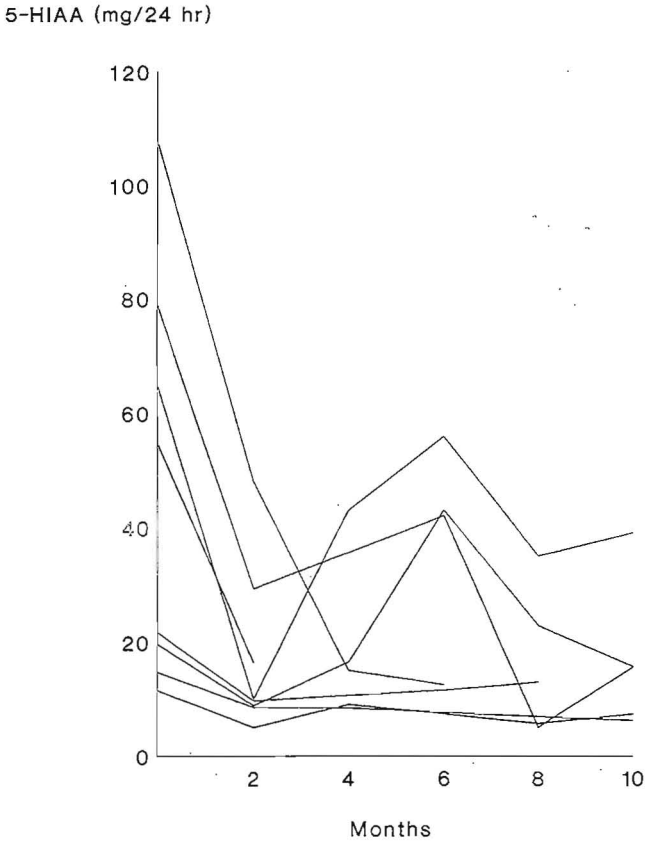

Figure 1. Behavior of 5-HIAA (mg/24 h) urinary levels in eight patients with a biochemical response.

Table 4. Side Effects of Interferon Treatment in 49 Evaluable Patients

World Health Organization grade	No. of patients			
	Grade 1	*Grade 2*	*Grade 3*	Overall
Fever	20	9	3	32
Chills	7	5	3	15
Myalgia	14	10	6	30
Leukopenia	18	12	3	33
Liver dysfunction	—	1	1	2
Anorexia	11	10	9	30
Nausea	14	1	1	16
Fatigue	14	10	9	33
Headache	8	4	2	14

Table 5. Responses to the Protocol Programs

Treatment	No. of evaluable cases	Response	
		Complete + partial	*Complete*
Interferon	49	5	1
I^{131} MIBG	3	1	—
Streptozocin + epirubicin	15	1	—

MIBG: metaiodobenzyl-guanidine.

ity of this type of neoplasm. We observed five objective tumor responses. Four PR occurred in patients with carcinoid tumors affected by carcinoid tumors with liver metastasis and high-urinary 5-HIAA levels. A CR was observed in one patient affected by MTC with mediastinal nodes.

Previous experience in the treatment of MTC with chemotherapeutic agents remains extremely limited, and the results are subject to debate. A review of reports, including cases treated with doxorubicin alone or in combination with other agents, indicated that about 20% of patients with MTC can be expected to obtain an objective response.[24] Experience in the treatment of MTC with other drugs is even more limited than experience with doxorubicin, and no conclusions can be drawn. Grohn et al. used low-dose rIFN-alpha-2a to treat two patients with previously treated advanced MTC.[25] No change in the size of measurable metastases was observed, despite a decrease in calcitonin values and a clear subjective improvement. However, given the small number of investigated patients, further studies are necessary to evaluate the efficacy of IFN in MTC.

Our study confirms the efficacy of rIFN-alpha-2a in patients with carcinoid syndrome, with subjective relief of symptoms being obtained in 64% of patients. Noteworthy is the correlation among objective responses, symptomatic control, and a reduction in 5-HIAA levels. The side effects of our schedule were tolerable in most patients, and there was no life-threatening toxicity.

After IFN treatment, the activity of polychemotherapy was evaluated. The low-response rate obtained might be explained by the large number of treatments given before chemotherapy. Given the small number of treated patients, no conclusions can be drawn in relation to radiometabolic therapy, although our results appear interesting and worthy of further confirmatory studies.

We conclude that our schedule is effective in controlling carcinoid syndrome and that it can be recommended because of its good patient compliance. However, no significant impact on tumor growth was observed. It might be useful to combine IFN therapy with conventional cytotoxic chemotherapy to improve objective responses in neuroendocrine tumors; some recent reports have suggested the activity of high doses of long-acting somatostatin analogues in the management of such tumors,[26–28] although the best dose and the most adequate schedule of administration have not yet been defined. In our institute, a study is in progress to evaluate the efficacy of such an agent on tumor growth inhibition.

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