Acta Oncologica Vol. 30 No. 5 1991

FROM THE DEPARTMENT OF INTERNAL MEDICINE, CANCER RESEARCH, UNIVERSITY OF ESSEN, ESSEN, GERMANY.

TREATMENT OF METASTATIC CARCINOID TUMORS AND THE CARCINOID SYNDROME WITH RECOMBINANT INTERFERON ALPHA

C. DOBERAUER, B. MENGELKOCH, O. KLOKE, U. WANDL and N. NIEDERLE

Abstract

Fourteen patients with metastatic carcinoid tumors were treated with recombinant interferon alpha-2b at a dosage of 3–4 × 10^6 IU s.c. daily or every second day. No objective tumor regression was observed. Six out of 8 patients with carcinoids of the ileum and the caecum showed stable disease lasting for a median of 25 months (range 4–57). In 3 out of 6 patients with carcinoids of rectum, lung and of unknown primary site, stable disease was observed lasting for 2–7 months. The remaining patients had progressive disease. Six out of 9 evaluable patients had a more than 50% reduction of urinary 24 h 5-hydroxyindoleacetic acid excretion lasting for a median of 4 months (range 2–11). Decrease of flushing was noticed in 3 out of 6 evaluable patients and decrease of diarrhea in 5 out of 9 evaluable patients. In 4 patients dose reduction was necessary due to confusion and fatigue.

Key words: Carcinoid tumor, carcinoid syndrome, recombinant interferon alpha.

Malignant carcinoid tumors are uncommon and slow-growing neoplasms. The 5-year relative survival rate of 18% has been reported for patients with distant metastases (1). Patients may be disabled by tumor progression itself or by carcinoid syndrome, e.g. flushing, diarrhea, bronchospasm, and right ventricular failure. Chemotherapy is not very effective and tends to be rather toxic (2). In 1983, Öberg et al. (3) first reported on the activity of natural human leukocyte interferon in patients with malignant carcinoids and carcinoid syndrome. The current study has attempted to determine the therapeutic effects of human recombinant interferon alpha-2b in this disease.

Material and Methods

Since April 1984, 14 patients have entered the study. All patients had histologically confirmed metastatic carcinoid tumors with progressive disease, elevated urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA), and/or significant symptoms from their disease (Table 1).

Recombinant interferon alpha-2b (rIFN-α2b, Intron A, Schering-Plough, Kenilworth, USA) was given subcutaneously. One patient received 4 × 10^6 IU daily, 5 patients 3 × 10^6 IU daily and 8 patients 3 × 10^6 IU every other day. Therapy was continued until objective tumor progression or subjective increase of symptoms. History, physical examination, blood counts, blood biochemistry, 24 h urine collection for estimation of 5-HIAA, and tumor measurements by ultrasound, x-ray, and/or computerized tomography were repeated every 4 weeks for 3 months and quarterly thereafter.

Three categories of response were assessed:

Tumor response. Complete remission (CR), defined as complete disappearance of all known disease for a minimum of 1 month; partial remission (PR), defined as ⩾ 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 (SD), defined as < 50% decrease or < 25% increase in the size of measurable lesions; progressive disease (PD), defined as ⩾ 25% increase of any tumor manifestation or the appearance of new lesions.

Biochemical response. Partial remission (PR), defined as ⩾ 50% decrease in elevated urinary excretion of 5-HIAA for at least 1 month.

Symtomatic response. ⩾ 50% reduction in the frequency of flushing or diarrhea.

Submitted 14 September 1990.
Accepted for publication 2 December 1990.

Table 1

Characteristics of 14 patients with metastatic carcinoids

Male/female (n)	8/6
Age (years)	37–76 (median 61)
Performance status (ECOG)	1–3 (median 1)
Primary site (n)	
Ileum	7
Caecum	1
Rectum	1
Lung	3
Unknown	2
Metastatic sites (n)	
Liver	13
Peritoneum	8
Lymph nodes	7
Lung	1
Bone	3
Other	2
Carcinoid syndrome (n)	
Elevated 5-HIAA	11
Flushing	6
Diarrhea	9
Prior therapy (n)	
Chemotherapy	3
Hormonal	5
None	7

Table 2

Therapeutic results in 14 patients with metastatic carcinoids

Parameter	Patients evaluable (n)	Response (n)
Tumor measurement	14	0
Urine 5-HIAA	9	6
Flushing	6	3
Diarrhea	9	5
Performance status	14	3

Results

Therapeutic response. All patients were evaluable for tumor response (Table 2). The median duration of interferon therapy was 4 months (range 2–57). No objective tumor remission was observed. Six out of 8 patients with carcinoids of the ileum and the caecum (midgut) showed SD lasting for a median of 25 months (range 4–57). In 3 out of 6 patients with carcinoids of the rectum, the lung or of unknown primary site, there was SD lasting for 2, 2 and 7 months respectively. The remaining patients had PD. In 6 out of 9 evaluable patients, pretreatment urine 5-HIAA elevation was reduced to more than 50% during therapy with a median duration of 4 months (range 2–11). In two patients with elevated 5-HIAA level before treatment, this parameter was not subsequently measured and the patients therefore excluded from this analysis. Symptomatic responses lasted for 4, 20 and 35 months in 3 out of 6 patients with flushing and 1–20 months (median 3 months) in 5 out of 9 patients with diarrhea. The performance status improved in 3 out of 14 patients.

Survival. Median survival of patients with midgut carcinoids was 48 months (range 9–93) from diagnosis of metastases and 38 months (range 3–59+) from start of interferon therapy. In patients with other types of carcinoids, median survival was 10 months (range 6–108) from the diagnosis of metastases and 7 months (range 3–16) from start of interferon therapy. The patients with PD died 3–7 months (median 4) after start of interferon treatment.

Adverse effects. Flu-like symptoms and fatigue were commonly observed. Dose reduction of rIFN-α2b to 2×10^6 IU every other day was necessary due to confusion in one patient and to severe fatigue in 3 patients. Leukocytopenia (WHO I) occurred in 6 patients and thrombocytopenia (WHO I) in one patient.

Discussion

The present investigation confirms that recombinant α-interferon has therapeutic activity in patients with metastatic carcinoids and carcinoid syndrome. Patients with midgut carcinoids achieved tumor stabilization and hormonal response more frequently and for a longer duration compared to the remaining patients with rectal and pulmonary carcinoids or carcinoids of unknown primary site. Due to the small number of patients no conclusions can be drawn concerning a possible relation between pretreatment status, dosage of interferon and response. Our results are comparable with those previously reported using natural and recombinant human alpha interferons (3–8). The low-dose regimen utilized in the present trial seems to be sufficient for inducing tumor stabilization, biochemical response, and symptomatic improvement. The toxicity was tolerable. Treatment with interferons represents an useful alternative for the medical management of patients with midgut carcinoids and the carcinoid syndrome (perhaps especially midgut carcinoids) and should be preferred to presently available cytotoxic chemotherapy.

Corresponding author: Dr. Claus Doberauer, Medizinische Klinik, Ruhr-Universität Bochum, Marienhospital, Hölkeskampring 40, D-4690 Herne 1, Germany.

REFERENCES

1. Godwin JD. Carcinoid tumors. An analysis of 2837 cases. Cancer 1975; 36: 560–9.
2. Bukowski RM, Johnson KG, Peterson RF, et al. A phase II trial of combination chemotherapy in patients with metastatic carcinoid tumors. Cancer 1987; 60: 2891–5.
3. Öberg K, Funa K, Alm G. Effects of leukocyte interferon on clinical symptoms and hormone levels in patients with midgut carcinoid tumors and the carcinoid syndrome. N Engl J Med 1983; 309: 129–33.

4. Öberg K, Norheim I, Lind E, et al. Treatment of malignant carcinoid tumors with human leukocyte interferon: long-term results. Cancer Treat Rep 1986; 70: 1297–304.
5. Öberg K, Alm G, Magnusson A, et al. Treatment of malignant carcinoid tumors with recombinant interferon alpha-2b: development of neutralizing interferon antibodies and possible loss of antitumor activity. J Natl Cancer Inst 1989; 81: 531–5.
6. Smith DB, Scarffe JH, Wagstaff J, Johnston RJ. Phase II trial of rDNA alpha 2b interferon in patients with malignant carcinoid tumor. Cancer Treat Rep 1987; 71: 1265–6.
7. Nobin A, Lindblom A, Månsson B, Sundberg M. Interferon treatment in patients with malignant carcinoids. Acta Oncol 1989; 28: 445–9.
8. Moertel CG, Rubin J, Kvols LK. Therapy of metastatic carcinoid tumor and the malignant carcinoid syndrome with recombinant leukocyte A interferon. J Clin Oncol 1989; 7: 865–8.