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COMBINED ALPHA- AND GAMMA-INTERFERON THERAPY FOR MALIGNANT MIDGUT CARCINOID TUMORS

A phase I–II trial

EVA TIENSUU JANSON, HANNA-LEENA KAUPPINEN and KJELL ÖBERG

A phase I–II trial was initiated to investigate the effects of a combination of alpha- and gamma-interferon in 12 patients with malignant carcinoid tumors. All patients were treated with alpha-interferon at a dose of 5–10 MU, 3–5 times weekly for a median of 22 months and had stable or progressive disease. Gamma-interferon was added at a daily dose of 0.5 MU subcutaneously. After 3 months of treatment 4 patients showed progressive biochemical disease while 8 patients had continuous stable biochemical disease. The dose was escalated to 1 MU daily in 8 patients while 3 continued at lower dose levels. Gamma-interferon was withdrawn from one patient due to mental depression. At 6 months there was 1 partial response, 3 patients with progressive and 7 with stable disease. Half of the patients experienced increased fatigue during the study. Other adverse reactions were skin lesions and myalgia. The combination therapy demonstrated subjective improvement in half of the patients, but lacked antitumoral effects.

Patients with malignant midgut carcinoid tumors who present liver metastases and carcinoid syndrome can usually be managed clinically for many years by treatment with alpha-interferons (1) and somatostatin analogs (2). Eventually though, progress of disease either by biochemical markers, tumor mass or symptoms, cannot be controlled by these drugs in escalated doses and new treatment alternatives are needed (3).

Since this group of patients respond to alpha-interferon it has been tempting to try other cytokines. Gamma-interferon acts through a receptor different from alpha-interferon and a combination of these two interferons might improve the therapeutic results. Gamma-interferon has, with promising results (4), been used in phase II trials for treatment of renal cell carcinoma. This has encouraged us to initiate a phase I–II trial in patients with malignant carcinoid tumors who demonstrated progressive disease or had had stable disease for at least 6 months during treatment with alpha-interferon. Those patients were given natural gamma-interferon in addition to the previous alpha-interferon treatment which was kept unchanged.

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From the Department of Internal Medicine, University Hospital, Uppsala, Sweden (E. Tiensuu Janson, K. Öberg) and Finnish Red Cross, Helsinki, Finland (H.-L. Kauppinen).
Correspondence to: Dr Eva Tiensuu Janson, Department of Internal Medicine, Akademiska sjukhuset, S-751 85 Uppsala, Sweden.
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Material and Methods

Patients. In this trial 12 patients, 7 males and 5 females with a median age of 56 years (range 43–71), were included. The median duration of disease before start of gamma-interferon treatment was 38 months (range 14–196). All patients had histopathologically verified carcinoid disease with liver metastases seen on computed tomography (CT). All patients had increased U-5-HIAA with a median of 436 μmol/l/24 h, range 128–1 639, (normal range 10–80 μmol/l/24 h). Eleven of the 12 patients had carcinoid syndrome with flushes and/or diarrhea (Table 1).

Treatment. To enter this trial the patients had to have been treated with alpha-interferon for at least 6 months.

Table 1

Patient characteristics

No. of patients	12
Males/females	7/5
Median age (years)	56 (43–71)
Median duration of disease (months)	38 (14–196)
Liver metastases	12/12
Carcinoid syndrome	11/12
Median U-5-HIAA (μmol/1/24 h)	436 (128–1 639)

At the time of inclusion in the study the patients either had to demonstrate progress of tumor size or increase in biochemical markers, or to have stable disease with high levels of U-5-HIAA and large liver metastases for the last 6 months. The patients received natural gamma-interferon (supplied by the Finnish Red Cross, Helsinki, Finland) at a dose of 0.5 MU daily as a subcutaneous injection in addition to their previous alpha-interferon treatment. The median dose of the alpha-interferon treatment was 30 MU weekly (6 MU injected subcutaneously 5 days a week) with a range of 15–35 MU. The duration of the initial alpha-interferon treatment was median 22 months, range 12–78. After 3 months of treatment the dose of gamma-interferon was increased to 1 MU daily if the patient had not responded. The final evaluation was made after 6 months of treatment.

Monitoring. Patients were monitored before the study was started and at 1, 3 and 6 months for routine hematology, liver and kidney function, blood glucose, serum electrolytes and urinary 5-HIAA, which was determined according to method described earlier (5) and calculated as a mean of two 24-h urine collections. Serum neopterin was also measured using a commercially available radioimmunoassay method from Henning, Berlin, Germany at the same time intervals. Tumor size was monitored by CT and ultrasound investigations before the study and at 3 and 6 months.

Response criteria. A complete biochemical response was defined as a normalization of the tumor marker U-5-HIAA, while partial biochemical response was considered when U-5-HIAA was reduced by 50% or more. An increase in U-5-HIAA of 25% or more was regarded as tumor progression. Reduction in tumor size, calculated as the product of two perpendicular diameters of the two largest metastases by more than 50%, was considered partial response while an increase by more than 25% was designated tumor progression.

Results

After 3 months of treatment all patients were eligible for evaluation. However, in one patient the initial dose of 0.5 MU daily had to be decreased to 0.25 MU daily due to severe tiredness and myalgia. Of the 12 patients included, 7 showed stable biochemical disease after 3 months of treatment while 5 patients progressed biochemically. Tumor size remained unchanged in 11 patients while one patient showed a significant increase in tumor size during the same period of time. Concerning symptomatic responses, 4 of 8 patients with flushes showed an improvement while 4 remained unchanged. Three of 6 patients suffering from diarrhea reported a relief of this symptom while one experienced a worsening of the diarrhea.

At 3 months the dose of gamma-interferon was increased to 1 MU daily in 8 patients. Three patients continued with the previous dose while one patient had to be withdrawn from gamma-interferon treatment due to mental depression. At 6 months there was 1 partial biochemical response, 7 patients showed continuous stable disease, and 3 had progressive biochemical disease. Tumor size remained unchanged in all but one patient who continued to progress. Four patients had a decrease in the number of flushes, while only one patient experienced an improvement of the diarrhea. Two patients had increasing symptoms of diarrhea while the rest of the patients felt no change of their symptoms.

Serum neopterin levels were tested before and during treatment. Only 4 patients showed a more than 2-fold increase in s-neopterin. Of these, 2 had progressive disease and 2 stable disease. Thus, the only objectively responding patient showed no induction of s-neopterin (Table 2).

Adverse reactions are summarized in Table 3. In short, about half of the patients suffered from fatigue, and the same proportion of patients complained of increasing muscle pain. Other problems were lethargia, dryness of mouth and skin, fever reactions and mental disturbances.

Table 2

Induction of serum neopterin in individual patients related to response

Pat. No.	S-neopterin level*		Response**
	before treatment	during treatment	
1	9.4	9.7	SD
2	2.5	4.1	SD
3	4.4	5.8	SD
4	2.8	3.7	SD
5	4.1	10.7	SD
6	5.7	7.0	SD
7	4.2	8.5	PD
8	7.3	13.2	PD
9	6.3	8.9	PR
10	2.3	4.0	SD
11	1.0	27.7	SD
12	1.3	31.0	PD

* nmol/l

** PR: partial response, SD: stable disease, PD: progressive disease

Table 3

Adverse reactions

	3 months	6 months
Fatigue	5	5
Myalgia	5	–
Lethargia	3	1
Dry mouth, eyes	3	2
Fever	1	–
Mental depression	1	–

Conclusion

In this phase I–II trial, 12 patients were treated with a combination of alpha-interferon and natural gamma-interferon. Only one patient had a significant reduction in U-5-HIAA after 6 months of treatment and 3 patients progressed. Nobody showed any reduction in tumor size. However, the addition of gamma-interferon seems to have been of some benefit to this group of patients since half of the patients experienced a relief of their symptoms of the carcinoid syndrome. One patient had to discontinue the treatment due to mental depression after 3 months and dose escalation was possible in 8 patients only. However, these 8 patients could tolerate 1 MU of natural gamma-interferon for at least 3 months despite high doses of alpha-interferon.

Adverse reactions, including fatigue, muscle pain and dryness of eyes, mouth and skin were quite pronounced. All these adverse reactions are well known to be associated with treatment with alpha-interferon and it seems probable that gamma-interferon potentiates these adverse reactions. Only four patients demonstrated a 2-fold induction of s-neopterin which might indicate that the doses used were too low. On the other hand, the patient demonstrating partial remission had no increase of s-neopterin, and we were thus not able to correlate the clinical response to induction of s-neopterin. Still, we doubt that a higher dose schedule should prove more efficient since the number and severity of the adverse reactions probably would have increased. This regimen demonstrated a subjective improvement in 50% of the patients but lacked antitumoral effect. However, an antitumoral effect cannot be ruled out if the combination is used in patients with less advanced stages of disease in other dosages or schedules.

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