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EXTENDED EXPERIENCE WITH RECOMBINANT α-2b INTERFERON WITH OR WITHOUT HEPATIC ARTERY EMBOLIZATION IN THE TREATMENT OF MIDGUT CARCINOID TUMOURS

A preliminary report

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Abstract

Thirty-six patients with histologically verified midgut carcinoid tumours and liver metastases were included in a prospective study with daily interferon therapy 5×10^6 IU s.c. for one or two years. All had the primary tumour removed at laparotomy, and whenever technically possible, an embolization of the hepatic arteries was performed prior to interferon start. Recombinant human α2b interferon from Schering-Plough was employed. When interferon was given alone, 24% responded after one year, judged from a 50% reduction in excretion of 5-hydroxyindoleacetic acid in the urine. Three patients had died. Stable disease was found in 43%, while 19% progressed. Survival rate was 40% after 5 years from start of therapy. The median survival time from start of therapy was 3 years and 4 months. When embolization of the liver arteries had been performed prior to the start of interferon treatment, the response rate was 60% after one year, 20% had stable disease and 20% progressed. Survival rate was 75% up to 5 years of observation. We conclude that interferon is an effective treatment of malignant metastatic midgut carcinoid and that survival might be prolonged compared with historical controls. Embolization of the liver arteries seems to increase the response rate after one year. Kaplan-Meier plots suggest prolonged survival when interferon treatment is combined with embolization.

Key words: Carcinoids, embolization of liver arteries, interferon, surgery.

Treatment of the carcinoid syndrome (1) with flush, diarrhoea, broncho-constriction, oedema, right ventricular failure and skin lesions is still subject to debate. The term malignant carcinoid syndrome is used when in addition increased excretion of 5-hydroxyindoleacetic acid (5-HIAA) in the urine and liver metastases are found (2). A mean time from onset of symptoms to death of 8.6 years, (range 6 months–29 years) has been reported (2). Moertel's data of patients with malignant carcinoid syndrome showed a median survival of 38 months from the first flush. However, in patients with high urinary excretion of 5-HIAA, it was only 14 months and if carcinoid heart disease was present 11 months (3).

It is generally accepted that surgical removal of the primary carcinoid tumour is desirable (3). Cytostatic treatment has only induced short remissions. Hepatic artery embolization (4–7) has been successfully used to reduce the hepatic metastases. Öberg et al. (8) first reported on the use of human lymphoblastoid interferon in carcinoid patients. We have since reported on the effect of recombinant interferon α-2b (rIFN-α2b) in patients with malignant carcinoid syndrome after one year's treatment (9). Somatostatin has been shown (10) to inhibit the carcinoid flush, and its long-acting analogue Sandostatin (SMS 201–995, Sandoz Ltd) can even reverse a carcinoid crisis (11) and might have beneficial effects on the malignant carcinoid syndrome (12).

We report now on five years' experience of interferon treatment of malignant midgut carcinoid tumours with liver metastases. After surgical removal of the primary

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tumour, daily interferon injections were given for one or two years, with or without a preceding embolization of the liver arteries. Some patients continued with interferon for a longer time.

Material and Methods

Thirty-six patients (27 females, 9 males) with histologically proven midgut carcinoids were included in the study. They all had malignant carcinoid syndrome (2), flushing and/or diarrhoea. The urinary excretion of 5-HIAA (13) was $\geqslant 56\ \mu mol \times 24\ h^{-1}$, which is twice the upper normal limit (95% confidence limit) in our laboratory. Hepatic metastases were demonstrated on (CT) in all patients.

Response criteria were defined according to the WHO recommendations. Response was defined as $\geqslant 50\%$ reduction, and progressive disease as $\geqslant 25\%$ increase in the response parameter, which was urinary 5-HIAA excretion.

The response was evaluated every 6 months. Patients were included in the study on an 'intention to treat basis', when interferon treatment was started. The patients remained in that group, even though temporary intermissions of medication occurred in some of them. Interferon treatment was stopped permanently in a few patients.

The treatment was based on the combination of surgical removal of the primary tumour(s), embolization of the liver arteries, and interferon treatment.

Surgery. Patients who had not had previous surgery of the primary tumour were laparotomized and as much tumour tissue as possible was removed.

Embolization of the liver arteries was performed in all patients where this was technically feasible, and where no contraindication was present (i.e. occlusion of the portal vein, cirrhosis of the liver, jaundice, cholangitis, or septicaemia). The technique has been described previously (9).

Interferon treatment consisted of rIFN-α2b produced by *Escherichia coli* bacteria (interferon alpha-2b, Intron A, Schering-Plough Corp., Kenilworth, NJ). Interferon treatment was started 2 weeks to 3 months after embolization of the liver arteries, or if embolization was not performed, after surgery or inclusion into the study. Intron was given daily subcutaneously in a dose of 5×10^6 IU by the patient after proper instruction. If the white blood count (WBC) fell below $2 \times 10^9 \times l^{-1}$, the dose was reduced at the investigator's discretion so that the WBC would stay above this value. If this was not possible, interferon treatment was discontinued for a period or permanently. Alternative treatment was given when the employed treatment had no effect and the patient was deteriorating.

Cytostatic treatment was employed when progressive disease was found. Streptozocin, Zanosar (Upjohn, Kalamazoo, MI) 1 g per day for 5 days and doxorubicin, Adriamycin (Carlo Erba, Milan, Italy) $40\ mg \times m^{-2}$ on day 3 constituted the induction regimen. Thereafter, every 3 weeks streptozocin 2 g and doxorubicin $40\ mg \times m^{-2}$ were given i.v. on the same day for 3 or 6 months.

Somatostatin analogue SMS 201-995 (Sandostatin) was given when symptoms were intolerable. Doses of 50 to 200 μg per day were used.

Irradiation treatment was used when metastases (especially bone metastases) produced intolerable pain or other symptoms.

Results

The Kaplan-Meier plots showed that median survival on interferon alone was 3 years and 4 months from the start of interferon treatment. After five years, 40% of the patients were alive. Before start of treatment median duration of symptoms was 0.9 years and median time since diagnosis 0.7 years.

When additional embolization procedure had been performed before start of interferon treatment, 75% of those patients were alive after 5 years. However, the observation period was too short to give a median survival time, due to the low death rate. Before start of treatment the median duration of symptoms was 2.5 years and time since diagnosis 0.9 years in this group of patients. The one-year response rate for urinary excretion of 5-HIAA was 24% when interferon was given alone, while it was 60% when prior embolization had been performed (Table 1).

When interferon treatment was discontinued after one year, due to randomization in responders ($n = 4$) or for any other reason ($n = 6$), the median 5-HIAA excretion increased by 281% and 143% respectively (Table 2). On the other hand, those who continued treatment ($n = 12$) showed no change after an additional 6 months (-1% and $+11\%$ respectively). This difference was significant ($p = 0.038$, Mann-Whitney).

Discussion

We have studied a defined subgroup of carcinoid tumours, namely histologically proven midgut carcinoids with liver metastases and carcinoid syndrome. Any comparison with historical data on treatment effects and survival must be made with this in mind. As historical control one might, however, use the calculated median survival time, 2.5 years for patients with liver metastases and carcinoid syndrome (14). It must then be remembered, that our survival data are calculated from start of therapy, that is the time from first symptoms or time from diagnosis must be added to our survival time.

Urinary excretion of 5-HIAA is the most accepted tumour marker for metastatic midgut carcinoid tumours (13). However, it is not always correlated with the patient's symptoms. Flushing may be better correlated with circulating levels of tachykinins, e.g. substance-P related peptides like neuropeptide K and neurokinin A (15-16),

Table 1

Results in patients after daily interferon treatment for one year, with or without prior embolization of liver arteries. Only patients observed for one year are included

	Interferon + embolization n = 10				Interferon only n = 21			
	Dead	Response	Stable	Progress	Dead	Response	Stable	Progress
Months								
6	0	7	3	0	0	8	8	5
12	0	6	2	2	3	5	9	4

Table 2

The effect of discontinuation of interferon treatment at 12 months as compared to continued treatment: Median urinary excretion of 5-HIAA in μmol/24 h

Treatment	No.	Start	6 months	12 months	18 months	Change
Continued	12	526	338	336	373	+11%
Discontinued	6	637	193	166	403	+143%

while diarrhoea might be more correlated with serotonin (17–18). It is possible that carcinoid cardiac disease is correlated with the excretion of 5-HIAA and levels of circulating tachykinins, but this still remains conjectural.

Resection of the primary tumour often results in symptomatic relief of shorter or longer duration in some patients with midgut carcinoids even in the presence of liver metastases. However, the literature does not allow any definite conclusions on the effect of this treatment (3). If the primary tumour is not removed, treatment with interferon might cause tumour shrinkage and obstruction of the intestine, thus indicating that the primary tumour should be removed. Reduction of tumour mass is generally believed to be of benefit in cancer treatment. Our experience supports the view that aggressive surgery prolongs survival (19).

Hepatic arterial embolization has been used to treat hepatic metastases from carcinoids by several groups (4–7). It requires a specially trained radiologist, and even in trained hands complications occur, some of them fatal (3). All our embolized patients were alive after one year (20), but some had a prolonged recovery including liver abscess formation. On the other hand, there was a higher response rate in this group than in those receiving interferon alone. Our groups are small and further studies are necessary to define the role of embolization in combination with other treatment schedules.

Interferon treatment has been proved effective in a series of patients by the Uppsala group using human lymphoblastoid interferon (8), or recombinant α2b interferon. Our results show a high response rate, particularly when interferon is combined with embolization.

The exact mechanism of action of IFN in carcinoid tumours as well as in other malignancies is not known. There are three main possibilities. Firstly an inhibition of cell division, secondly a regulation of oncogene expression, and thirdly recruitment of immune responses (21, 22). A remarkable abnormality has been found in carcinoid patients: a deficient IFN response of natural killer cells (NK cells) to stimulation by SACoI and an influence of IFN therapy on several parameters of the interferon-NK cell system. In addition interferon can also activate macrophages for antitumour cytotoxic activity. The possibility exists that endogenous interferons take part in natural antitumour activity. It is not known why some tumour types respond to interferon while others do not.

Side-effects of interferon were tolerable in most patients, but nearly all patients were aware of fatigue, especially when they recovered from it after discontinuation of therapy. The transitory fever and malaise at the induction of therapy troubled only one patient. In conclusion the side-effects were common, transient and immediately reversible upon treatment discontinuation.

The immunologic side-effects of interferon treatment are at present not fully understood. The increase in immunoglobulin concentration might be part of the therapeutic principle, along with the increase in circulating immune complexes. The tendency to positive antinuclear antibodies might be clinically significant. We experienced hypothyroidism, sometimes preceded by transient hyperthyroidism together with positive thyroid antibodies. These complications were regarded as secondary to the immune modulating effect of interferon, but we do not yet know

whether they will be permanent. Substitution of thyroxine reversed the clinical symptoms.

There seems to be tachyphylaxis to several of the side-effects of IFN, especially the initial flu-like complaints and fever (23). We also experienced this phenomenon, and the hair loss during therapy ended spontaneously. Fatigue was felt by many patients, and bedtime administration was therefore preferred. Using very high doses, exceeding ours by a factor of 20, Quesada et al. (23) noticed psychotic behaviour and expressive aphasia. Cutaneous side-effects like dry skin, exacerbation of psoriasis and enhanced radiation toxicity have recently been reported (24).

The addition of doxorubicin and streptozotocin did not significantly change the course in those with progressive disease. Whether this regimen could have had beneficial effects in the group as a whole was not studied. Sandostatin treatment seemed to reduce some of the symptoms in the most troubled patients for a period.

We have noticed that carcinoid patients given radiation therapy for painful skeletal metastases have shown increased radiation toxicity and that response rates were surprisingly high. This agrees well with the results in other tumours treated with interferon (25). The response of patients with malignant carcinoids to irradiation of the abdomen has not given conclusive results (26), while in others 25% response rates have been shown (27).

Our data indicate that interferon treatment is the most promising treatment today, especially when combined with embolization. We feel that it should be preceded by aggressive surgery. Certain tolerable side-effects are seen. The question whether immunologic side-effects are reversible after discontinuation merits further studies.

When interferon treatment is stopped, the disease seems to be reactivated. This means that our survival data are influenced by the fact that most patients were only treated for 1 to 2 years. Continuous treatment might have given longer survival, but we wanted to study the effect of treatment for only 1 to 2 years.

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REFERENCES

1. Biörck G, Axén O, Thorson Å. Unusual cyanosis in a boy with congenital pulmonary stenosis and tricuspid insufficiency. Fatal outcome after angiocardiography. Am Heart J 1952; 44: 143–8.
2. Davis Z, Moertel CG, McIlrath DC. The malignant carcinoid syndrome. Surg Gynecol Obstet 1973; 137: 637–44.
3. Moertel CG. Treatment of the carcinoid tumor and the malignant carcinoid syndrome. J Clin Oncol 1983; 1: 727–40.
4. Maton PN, Camilleri M, Grffin G, Allison DJ, Hodgson HJF, Chadwick VS. Role of hepatic arterial embolisation in the carcinoid syndrome. Br Med J 1983; 287: 932–5.
5. Mårtensson H, Nobin A, Bengmark S, Lunderquist A, Owman T, Sandén G. Embolization of the liver in the management of metastatic carcinoid tumors. J Surg Oncol 1984; 27: 152–8.
6. Mitty HA, Warner RRP, Newman LH, Train JS, Parnes IH. Control of carcinoid syndrome with hepatic artery embolization. Radiology 1985; 155: 623–6.
7. Stockmann F, Creutzfeldt W. Approach to hepatic involvement by endocrine tumors of the gastrointestinal tract. Semin Liver Dis 1988; 8: 254–62.
8. Öberg K, Funa K, Alm G. Effects of leukocyte interferon on clinical symptoms and hormone levels in patients with midgut carcinoid tumors and carcinoid syndrome. N Engl J Med 1983; 309: 129–33.
9. Hanssen LE, Schrumpf E, Kolbenstvedt AN, Tausjø J, Dolva LØ. Treatment of metastatic midgut carcinoid tumours with recombinant human α2b interferon with or without prior hepatic artery embolization. Scand J Gastroenterol 1989; 24: 787–95.
10. Froelich JC, Bloomgarten ZT, Oates JA, McGuigan JE, Rabinowitz D. The carcinoid flush. Provocation by pentagastrin and inhibition by somatostatin. N Engl J Med 1978; 299: 1055–7.
11. Kvols LK, Martin JK, Marsh HM, Moertel CG. Rapid reversal of carcinoid crisis with a somatostatin analogue. N Engl J Med 1985; 313: 1229–30.
12. Kvols LK, Moertel CG, O'Connell MJ, Schutt AJ, Rubin J, Hahn RG. Treatment of the malignant carcinoid syndrome: evaluation of a long-acting somatostatin analogue. N Engl J Med 1986; 315: 663–6.
13. Feldman JM. Urinary serotonin in the diagnosis of carcinoid tumors. Clin Chem 1986; 32: 840–4.
14. Moertel CG, Sauer WG, Dockerty MB, Baggenstoss AH. Life history of the carcinoid tumor of the small intestine. Cancer 1961; 14: 901–12.
15. Theodorsson-Norheim E, Norheim I, Öberg K, et al. Neuropeptide K: a major tachykinin in plasma and tumor tissues from carcinoid patients. Biochem Biophys Res Commun 1985; 131: 77–83.
16. Norheim I, Theodorsson-Norheim E, Brodin E, Öberg K. Tachykinins in carcinoid tumors: their use as a tumor marker and possible role in the carcinoid flush. J Clin Endocrinol Metab 1986; 63: 605–12.
17. Jaffe BM. Prostaglandins and serotonin: nonpeptide diarrheogenic hormones. World J Surg 1979; 3: 565–78.
18. Roberts WC, Sjoerdsma A. The cardiac disease associated with the carcinoid syndrome (carcinoid heart disease). Am J Med 1964; 36: 5–34.
19. Søreide O, Berstad T, Bakka A, et al. Surgical treatment as a principle in patients with advanced carcinoid tumors. Surgery 1991; (in press).
20. Kolmannskog F, Kolbenstvedt AN, Schrumpf E, Hanssen LE. Side-effects and complications following hepatic artery embolization in carcinoid syndrome. Scand J Gastroenterol 1991; 26: (in press).
21. Hersey P. The evolving role of alpha interferon in the treatment of malignancies. Aust NZ J Med 1986; 16: 425–37.
22. Herberman RB. Cancer therapy by biological response modifiers. Drug Res 1987; 37: 246–50.
23. Quesada JR, Talpaz M, Rios A, Kurzrock R, Gutterman JU. Clinical toxicity of interferons in cancer patients: a review. J Clin Oncol 1986; 4: 234–43.

24. Bengmark S, Nobin A, Jepsson B, Tranberg KG. Transient repeated dearterialization combined with intraarterial infusion of oncolytic drugs in the treatment of liver tumors. Recent Results Cancer Res 1983; 86: 68–74.
25. Torristi J, Berg C, Bonnem E, Dritschilo A. The combined use of interferon and radiotherapy in cancer management. Semin Oncol 1986; 13 (Suppl. 2): 78–83.
26. Keane TJ, Rider WD, Harwood AR, et al. Whole abdominal radiation in the management of metastatic gastro-intestinal carcinoid tumor. Int J Radiat Oncol Biol Phys 1981; 7: 1519–21.
27. Samlowski WE, Eyre HJ, Sanse WT. Evaluation of the response of unresectable carcinoid tumors to radiotherapy. Int J Radiat Oncol Biol Phys 1986; 12: 301–5.