Interferon and meta-iodobenzylguanidin combinations in the treatment of metastatic carcinoid tumours

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Abstract

Interferon (IFN) and meta-iodobenzylguanidin (MIBG) are active in metastatic carcinoids. In a phase II study, we evaluated the effect upon diagnostic ¹³¹I-MIBG uptake and the clinical response of the combination.

¹³¹I-MIBG scintigraphy was performed prior to treatment, after 8 weeks of IFN and after unlabelled MIBG. The tumour over non-tumour (T/NT) ratios were quantitatively determined by comparing counts in the centre of the tumour (liver metastases) with those in an adjacent area of normal liver uptake (T/NT1) and with abdominal background area (T/NT2).

The T/NT1 ratio showed an increase of > 10% in only four out of 21 patients (19%) after IFN ($P = 0.178$) and significantly more often in nine out of 18 patients (50%) after unlabelled MIBG ($P = 0.016$). The absolute uptake in tumour deposits was also increased if compared with the abdominal background (T/NT2: 23% increase after IFN and 83% increase after unlabelled MIBG). The combination produced 91% of patients with stable disease (using World Health Organisation criteria) at computed tomography scan and a biochemical response (a reduction of at least 50% in urinary 5-hydroxyindolacetic acid excretion) in 39%.

IFN- α did not significantly improve tumour retention of ¹³¹I-MIBG. In contrast, unlabelled MIBG significantly improved biodistribution and tumour uptake in 83%. A synergistic effect was not seen.

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Introduction

Carcinoid tumours are neuroendocrine tumours associated with the synthesis and secretion of biologically active substances that can induce characteristic symptoms of the carcinoid syndrome (flushing, diarrhoea and wheezing). Metastatic disease at diagnosis is found in 22%, and is largely dependent on the primary localisation: appendix 1.5%, lung 4.8% and small and large bowel localisations 28% (excluding appendix and rectum) (Quaadvlieg *et al.* 2001). Various treatment strategies have been recommended, mainly aimed at amelioration of the incapacitating symptoms (Moertel *et al.* 1989, Oberg 1994). Surgery is indicated for the primary tumour in cases of obstruction.

In metastatic disease of the liver, palliative resection may be of value, but is usually not feasible because of diffuse involvement of both liver lobes. For medical treatment, somatostatin analogues and/or interferon (IFN)- α formulations are employed by many clinicians, as biochemical and subjective responses are observed in 70% and 80% respectively for somatostatin analogues (Harris & Redfern 1995) and 40% and 70% respectively for IFN- α formulations (Oberg *et al.* 1994). Pharmacological doses of meta-iodobenzylguanidin (MIBG) resulted in symptomatic improvement in 60% of carcinoid patients (Taal *et al.* 1996). The cytotoxic effect of MIBG is related to the inhibition of mitochondrial respiration and is dependent on anaerobic glycolysis, resulting in enhanced glucose

consumption, increased lactic acid production, inhibition of oxygen consumption and decreased adenosine triphosphate levels (Kuin *et al.* 1994). Another possibility is treatment with radiolabelled MIBG, based on a positive scintigraphy which leads to long-term palliation in 60% of patients. Although reduction in tumour growth is rarely reported, stable disease is described in a substantial proportion of the patients (Taal *et al.* 1996, 2000, Caplin *et al.* 1998, Mukherjee *et al.* 2001, Pathirana *et al.* 2001). Worldwide experience with ^{131}I -MIBG diagnostic imaging has indicated a cumulative sensitivity of 70% in 237 patients with carcinoid tumours (Hoefnagel 1991). Predosing with unlabelled MIBG resulted in improved tumour targeting, biochemical response and hence prolonged palliation (Zuetenhorst *et al.* 1999, Taal *et al.* 2000). Carcinoids are known to take up amino acid precursors for the endogenous production of serotonin. Recent reports suggest a role of vesicular monoamine transporters in this uptake (Eissele *et al.* 1999, Kolby *et al.* 2003). Pretreatment with unlabelled MIBG can produce a saturation of normal tissues with a preferential binding of the radioactive labelled MIBG to carcinoid tumour cells. Another option to increase MIBG tumour targeting might be pretreatment with $\text{INF-}\alpha$. This assumption is based on the laboratory findings of an improved uptake of ^{125}I -MIBG following $\text{INF-}\gamma$ administration in neuroblastoma cell lines. This phenomenon was based on *de novo* synthesis of MIBG receptor transporters (Montaldo *et al.* 1992). Although $\text{INF-}\alpha$ is different from $\text{INF-}\gamma$, differentiation of carcinoid tumour cells with the application of $\text{INF-}\alpha$ has been described, with good clinical results (Oberge 1992). It was hypothesised that the combination of two active treatment modalities (INF and MIBG) may lead to an additive or even synergistic effect.

In the currently presented phase II study, we examined the effect of $\text{INF-}\alpha$ upon diagnostic ^{131}I -MIBG uptake by carcinoid tumours, and whether the clinical response, including quality of life, to $\text{INF-}\alpha$ therapy was improved by MIBG. In addition $\text{INF-}\alpha$ antibody formation was evaluated for its influence on the results of the therapy.

Patients and methods

Patients

Patients who were referred to our hospital between October 1996 and December 1998 with metastatic carcinoid tumours, a World Health Organisation (WHO) performance status of 0–2 and normal blood cell counts and renal function were eligible. Twenty-six consecutive patients (18 men and eight women) entered the study (Table 1). All patients had metastatic, well-differentiated neuroendocrine tumours, originating from

the distal ileum-coecum ($n = 6$), the lungs ($n = 5$), the stomach ($n = 1$) or with an unknown primary site ($n = 14$). Median age was 63 years (range: 41–77). In 23 patients, the diagnosis of neuroendocrine tumour was confirmed by histology. In two patients, fine needle aspiration led to the diagnosis; one patient refused a biopsy and the diagnosis was based on strongly elevated urinary 5-hydroxyindolacetic acid (5-HIAA) excretion and symptoms. Three patients had normal urinary 5-HIAA excretions; median pretreatment urinary 5-HIAA excretion in the 23 secretors was $503\text{ }\mu\text{mol}/24\text{ h}$ (normal $<40\text{ }\mu\text{mol}/24\text{ h}$). Twenty-two patients (85%) suffered from the carcinoid syndrome with diarrhoea and/or flushes at the time of enrolment. Fifteen patients had complaints related to tumour size or localisation. Median duration of symptoms before the start of treatment was 7 months (range: 0–94 months). In 11 patients, the indication for enrolment was progression under systemic therapy and in two after prior surgery; the remaining patients were not pretreated. Four patients received prior treatment with unlabelled as well as ^{131}I -MIBG; the interval was at least 2.5 years. The study was approved by the local medical ethical committee and written informed consent was given by all patients.

Treatment

Treatment started with $\text{INF-}\alpha$ 2a (Roferon; Hoffmann-La Roche, Basel, Switzerland), 6 million IU thrice weekly s.c. After 8 weeks, unlabelled MIBG was added in three cycles of increasing doses (10, 20 and $40\text{ mg}/\text{m}^2$) in a 4-h infusion every 4 weeks as described earlier (Taal *et al.* 1996). Subsequently, patients with a positive ^{131}I -MIBG scan received two therapeutic doses of $7.4\text{ GBq }^{131}\text{I}$ -MIBG administered during a hospital stay (Taal *et al.* 1996). $\text{INF-}\alpha$ 2a therapy was continued for 6 months and only stopped if serious side-effects persisted or in cases of progressive disease. During this study, ten patients were treated with somatostatin analogues which were continued in a stable dosage.

Methods

The effect of $\text{INF-}\alpha$ upon ^{131}I -MIBG tumour uptake was evaluated by comparing ^{131}I -MIBG scans prior to and after 8 weeks of treatment. Subsequently, the effect of unlabelled MIBG was evaluated by the ^{131}I -MIBG scan directly following the infusion of unlabelled MIBG. The tumour over non-tumour (T/NT) ratio was quantitatively determined by comparing counts in the centre of the tumour (liver metastases) with those in an adjacent area of normal liver uptake (T/NT1) and with abdominal background area (T/NT2) as described earlier (Hoefnagel *et al.* 2000). In cases of extrahepatic tumour localisation, the

Table 1 Clinical characteristics of the patients

Total group of patients	26
Sex	
Male	18
Female	8
Age (years)	
Median (range)	63 (41–77)
Primary site	
Distal ileum-coecum	6
Lung	5
Stomach	1
Unknown	14
Therapy (no. of patients)	
None	14
Somatostatin analogues	10
IFN- α 2a	0
MIBG (> 2.5 years before study)	4
^{131}I -MIBG (> 2.5 years before study)	5
Chemotherapy	2
Radiotherapy (skin metastases)	1
Duration of symptoms before start of study (months)	
Median (range)	7 (0–94)
Predominant symptoms	
Fever/weight loss/sweating/fatigue	8
Carcinoid syndrome	14
Abdominal pain (unrelated to carcinoid syndrome)	3
None	1
Indication for starting the protocol	
First-line therapy	13
Progression under therapy	13
Urinary 5-HIAA excretion ($\mu\text{mol}/24\text{ h}$) at start of study	
<ULN ($n = 3$) median (range)	23 (21–34)
> ULN ($n = 23$) median (range)	503 (130–3131)

5-HIAA, normal <40 $\mu\text{mol}/24\text{ h}$; ULN, upper limit of normal.

ratio was calculated by comparing this particular localisation with the abdominal background (T/NT3). A 10% increase in biodistribution was considered a clinical important difference.

Computed tomography (CT) scans were performed before the start, after 8 weeks of IFN treatment and after the third course of unlabelled MIBG and after the last course of ^{131}I -MIBG. CT scans were systematically reviewed without clinical information to classify the liver metastases into two categories: nodular and diffuse. Objective responses by tumour size were assessed using the WHO criteria. Complete response: disappearance of all target lesions; partial response (PR): > 50% decrease of bi-dimensionally measured diameters; progressive disease (PD): > 25% increase in size of measurable lesions or appearance of a new lesion; stable disease (SD): neither PD nor PR. A biochemical response was defined as a reduction of at least 50% in urinary 5-HIAA excretion. Adverse effects were scored using the common toxicity criteria.

IFN- α 2a antibody concentrations before and after at least 4 months of IFN therapy were analysed using an

enzyme immunoassay method (Schellekens *et al.* 1997). An antibody titre rise was considered significant if the post-IFN value exceeded the 95th percentile of the groups' pre-IFN values, and the rise was at least 50% of the pre-IFN value.

The effect on quality of life was measured with the EORTC quality of life questionnaire QLQ-C30 (Wymenga *et al.* 1999, Langendijk *et al.* 2001). Questions were added to evaluate the specific carcinoid symptoms, such as flushes and abdominal cramps, and the specific side-effects of IFN such as chills and muscle pain. All scores were linearly converted to a 0–100 scale. For the functional and global health status/quality of life scales, higher scores represent a better level of functioning. For the symptom scales, higher scores represent a greater degree of symptoms. The Center for Epidemiologic Studies depression (CES-D) scale list of 20 items was included to measure depression (Radloff 1977). A score of 16 or more indicated depression (Geerlings *et al.* 2000, Sarna *et al.* 2002). Finally, the symptoms as noted by the physician in the medical record were evaluated. According

to these findings, patients were divided into four groups based on the predominant symptoms: (A) patients with the characteristic carcinoid syndrome of flushing, diarrhoea and/or wheezing; (B) patients with systemic symptoms such as fever, anorexia, sweating and/or fatigue; (C) patients with abdominal pain; (D) patients without symptoms. These main symptoms were considered to be improved if the patient experienced a clear reduction (e.g. weight gain or > 50% less additional medication) or disappearance of symptoms, and progression in cases of deterioration. Survival and time to progression (TTP) were measured from the start of treatment. TTP was defined as the number of months between start of IFN and a change in therapeutic regimen because of progression.

For statistical analysis, the two-sided, paired *t*-test was applied with a *P* value of 0.05 as the level of significance. Survival curves were constructed using the Kaplan–Meier method and compared using a log-rank test. Categorical differences between groups were compared using Fishers’ exact test. For all calculations SPSS 10.0 (SPSS Inc., Chicago, USA) was used.

Results

Protocol evaluation

Twenty-three patients completed the first 8 weeks of IFN therapy. Three patients stopped within 8 weeks because of clinical progression.

Twenty patients were able to complete the full-course of three MIBG cycles and reached follow-up at 21 weeks. Two patients were progressive between the first and the second treatment with MIBG. In one patient, the third treatment with MIBG was not administered as the previous two failed to achieve relief of symptoms.

Among the twenty patients who reached week 21, seven patients received two cycles of 7.4 GBq ¹³¹I-MIBG and fully completed the protocol. Seven patients received only one cycle of ¹³¹I-MIBG: two patients because of progressive disease, two patients based on thrombocytopenia, one patient pretreated with ¹³¹I-MIBG reached his cumulative maximal radiation dose, and in two patients a temporary drop in WHO performance status prevented further ¹³¹I-MIBG infusion. Six patients were not given

¹³¹I-MIBG as their ¹³¹I-MIBG scan was negative, but they continued IFN-α as planned.

Responses, TTP, survival and adverse effects

In 22 patients (85%) the tumour lesions remained stable at evaluation of the CT scan after 8 weeks of treatment with IFN, in one there was PD. In addition, three patients were rapidly progressive in terms of symptoms and 5-HIAA excretion and a follow-up CT scan was not performed. In one patient with no change at prior chemotherapy, the primary tumour showed PR, while the liver metastases remained stable. At 21 weeks, after three courses of unlabelled MIBG, two additional patients were clinically progressive and no follow-up CT scans were performed. The remaining 20 patients (91%) showed SD. At 34 weeks, after two courses of ¹³¹I-MIBG, two out of 20 patients were clinically progressive and a follow-up CT scan was not available. One had PD and 17 had SD. Therefore, none of the patients had a PR, defined by CT criteria and, after 34 weeks, 17 out of 26 (65%) patients had SD.

After 8 weeks of IFN therapy and using biochemical evaluation of urinary 5-HIAA excretion, PR values were reached in eight out of 23 (35%) patients with elevated urinary 5-HIAA. At 21 weeks, one additional patient who had previously shown SD reached PR. The protocol resulted in an overall best response rate (according to 5-HIAA excretion) of 39%.

The T/NT1 ratio of the ¹³¹I-MIBG retention showed a 10% increase in only four out of 21 patients (19%) after IFN treatment, while this was the case in nine out of 18 patients (50%) after unlabelled MIBG (Table 2). Using the T/NT2 ratio, these figures were even more pronounced: 23% after IFN and 83% after unlabelled MIBG (Fig. 1). This improved biodistribution was not merely based on a decrease in background activity in the liver, but the absolute uptake in tumour deposits was increased if compared with the abdominal background. Extra-hepatic tumour localisation was present in only seven patients and the T/NT3 ratio showed a similar effect after IFN and MIBG with 14% and 83% respectively. Overall, the changes after IFN treatment were not statistically sig-

Table 2 Changes in ¹³¹I-MIBG retention after IFN treatment and application of unlabelled MIBG

	T/NT1 ratio		T/NT2 ratio	
	After IFN	After MIBG	After IFN	After MIBG
> 10% increase in ¹³¹ I-MIBG uptake	4/21 (19%)	9/18 (50%)	5/21 (23%)	15/18 (83%)
No change in ¹³¹ I-MIBG uptake	16/21 (76%)	7/18 (39%)	10/21 (48%)	3/18 (17%)
> 10% decrease in ¹³¹ I-MIBG uptake	1/21 (5%)	2/18 (11%)	6/21 (29%)	0/18 (0%)

Figure 1 ^{131}I -MIBG scintigraphy before (pre-IFN) and after (post-IFN) treatment with IFN and after treatment with unlabelled MIBG (after cold MIBG). Uptake in liver metastases compared with normal liver tissue (T/NT1) and lung metastases compared with abdominal background (T/NT3) shows a minimal increase after IFN of 7% and 3% respectively. After application of unlabelled MIBG, uptake in both localisations was increased by 31% and 69% respectively. The quantitatively determined uptake by comparing counts in the centre of the tumour is represented below the scintigrams.

nificant ($P = 0.178$). In contrast, a significant ($P = 0.016$) increase after treatment with unlabelled MIBG was found.

The median TTP (Fig. 2) was 9 months and after 18 months 90% of the patients had PD. Median overall survival (Fig. 2) from the start of the present treatment protocol was 27 months, while the 5-year survival was 33%. In patients with an increased tumour retention at ^{131}I -MIBG scintigraphy after IFN, survival was comparable ($P = 0.89$) with the others (median 32 versus 38 months). Nor was there a difference in survival ($P = 0.80$) for patients with increased tumour retention induced by unlabelled MIBG ($n = 9$). The presence of diffuse versus nodular liver metastases did not result in a difference in survival. However, in pretreated patients, survival tended ($P = 0.20$) to be shorter compared with patients who were not pretreated (18 versus 37 months).

IFN-related toxicity was mild and transient: nine patients suffered from transient influenza-like symptoms

and eight from fatigue. Severe toxicity was seen in one patient suffering from grade III hypertension during unlabelled MIBG infusion and in one patient suffering from grade III thrombocytopenia after ^{131}I -MIBG infusion. One patient developed a carcinoid crisis following ^{131}I -MIBG infusion. All side-effects were reversible and there were no toxic deaths.

Antibodies against recombinant human IFN- α 2a and TTP

A second blood sample used for IFN- α antibody titre determination, taken 4–6 months after the start of the IFN treatment, was available in 19 patients with a median time of IFN treatment of 6.5 months (range: 4.1–9.2). Six of these 19 patients (32%) developed a rise in antibody titre. Patient characteristics, including gender, age, primary site, previous therapies, urinary 5-HIAA values and disease

Figure 2 Survival and TTP. Median TTP was 9 months, median survival was 27 months with a 5-year survival of 33%. Eight patients were still alive during the last follow-up.

duration at the start of the protocol were not significantly different between patients with and without development of antibodies. A difference in response and TTP was not found, but overall survival (Fig. 3) was significantly better in patients without antibody formation ($P = 0.04$).

Symptoms, quality of life and depression

As summarised in Table 3, quality of life measurement at week 8 with IFN monotherapy did not show significant changes in the five functioning scales. Among the additional single symptoms, flushes and worries about disease progression diminished statistically significant. At week 21, with unlabelled MIBG added to the IFN, appetite deteriorated gradually over time, but this difference was not significant ($P = 0.083$). Abdominal pain increased in the first 8 weeks and then returned to baseline in the subsequent weeks of MIBG treatment.

By comparing patients with predominantly carcinoid symptoms ($n = 14$) with patients complaining of other systemic symptoms, such as fever, severe anorexia and sweating ($n = 8$), tumour complaints showed differences in response on IFN and MIBG treatment. Half of the patients (50%) with carcinoid syndrome reported improvement after 8 weeks of IFN compared with four out of 14 (29%) following unlabelled MIBG ($P = 0.3$). Similarly, three out of eight (38%) patients with systemic symptoms mentioned improvement with IFN, but they did better after unlabelled MIBG with a response in six out of eight (75%) ($P = 0.14$). Overall, after MIBG treatment, patients with systemic symptoms responded

Figure 3 TTP according to the development of an IFN- α 2a titre rise after at least 3 months of IFN- α 2a treatment. In six out of 19 patients (32%), a rise in antibodies was observed. Difference in response and TTP were not found. Overall survival was significantly better in patients without antibody formation ($P = 0.04$).

significantly better on MIBG treatment compared with patients with carcinoid syndrome ($P = 0.04$).

Discussion

IFN- α formulations are well known for their therapeutic effect in metastatic carcinoid disease: subjective responses can be achieved in up to 70% of patients and biochemical responses are observed in 40–50% (Moertel *et al.* 1989, Oberg *et al.* 1994). A measurable tumour reduction was, however, only occasionally reported. The anti-proliferative effect of IFN- α has, at least in part, been ascribed to a delay in the S-G₂/M phase transit (Detjen *et al.* 2000). In agreement with the literature, the present study showed a biochemical response rate of 35% with IFN- α 2a monotherapy, but in one patient the primary tumour showed a PR, while the liver metastases remained stable. Side-effects were mild and limited to influenza-like symptoms and sometimes fatigue, both responded well to paracetamol.

In 32% of our patients, neutralising antibodies were detected during follow-up. The response to the treatment protocol and the TTP were not different, although the overall survival was worse in the presence of antibodies. However, the role of these antibodies is controversial as the presence of these antibodies is probably not related to the response to IFN administration, at least in patients

Table 3 Quality of life by EORTC QLQ-C30 and depression score by CES-D

	<i>n</i>	Baseline mean	S.D.	Mean change T ₀ –T ₈			<i>n</i>	Week 8 mean	S.D.	Mean change T ₈ –T ₂₁		
				Mean	S.D.	<i>P</i>				Mean	S.D.	<i>P</i>
Functioning scales ^a												
Physical functioning	20	79.3	17.3	–2.0	17.7	0.619	18	80.6	18.2	–3.1	12.2	0.290
Role functioning	20	74.2	27.8	–16.7	44.3	0.109	18	63.0	29.5	–1.9	26.1	0.767
Cognitive functioning	20	85.8	20.4	–1.7	20.2	0.716	18	86.1	14.3	–3.7	13.5	0.260
Emotional functioning	20	74.2	15.7	0.8	18.7	0.844	18	75.9	19.8	–4.6	12.9	0.145
Social functioning	20	83.3	18.7	–7.5	39.5	0.407	18	83.3	26.2	–0.9	18.5	0.834
Overall rating of quality of life ^a												
Global quality of life	20	65.0	18.5	–5.0	22.2	0.326	18	64.4	21.4	–0.9	13.1	0.767
Symptoms: scales and single items ^b												
Fatigue	20	32.2	24.2	7.2	23.2	0.179	18	35.8	20.0	3.1	19.0	0.500
Nausea and vomiting	20	4.2	9.2	5.0	15.4	0.163	18	7.4	11.7	2.8	10.3	0.269
Pain	20	19.2	23.7	–1.7	28.6	0.797	18	13.0	19.4	7.4	21.6	0.163
Dyspnoea	20	23.3	28.8	1.7	20.2	0.716	18	20.4	23.3	0	19.8	1.00
Insomnia	20	18.3	25.3	–3.3	32.3	0.649	18	9.3	19.2	9.3	27.5	0.172
Appetite loss	20	13.3	22.7	6.7	27.8	0.297	18	20.4	28.3	11.1	25.6	0.083
Constipation	20	3.3	14.9	5.0	12.2	0.083	18	3.7	10.8	0	11.4	1.00
Diarrhoea	19	33.3	29.4	–5.3	22.9	0.331	17	19.6	23.7	7.8	22.1	0.163
Financial impact	20	1.7	7.5	–1.7	7.5	0.330	18	0	0	1.9	7.9	0.331
Flushes	20	48.3	27.5	–15.0	27.5	0.025	18	27.8	23.6	1.9	26.7	0.772
Fevers	20	10.0	21.9	–8.3	23.9	0.135	18	1.9	7.9	0	11.4	1.00
Muscle pain	20	26.7	29.8	–1.7	29.6	0.804	18	22.2	19.8	7.4	29.3	0.298
Abdominal pain	18	14.8	20.5	9.3	27.5	0.172	17	23.5	30.7	–9.8	28.3	0.172
Worries about disease progression	20	60.0	23.2	–18.3	27.5	0.008	18	37.0	25.3	–3.7	19.4	0.430
Depression ^b												
CES-D	19	11.3	7.0	1.7	6.7	0.272	18	12.0	7.7	0.5	5.8	0.704

T₀–T₈; interval week 0–8, T₈–T₂₁; interval week 8–21.^aHigher score indicates better functioning: a negative change score is a deterioration in functioning, a positive change score an improvement.^bHigher score indicates more symptoms: a positive change score is an increase in symptoms, a negative change score a decrease.

with hepatitis B (Itri *et al.* 1989). This was confirmed in a more recent paper describing patients with hepatitis C treated with IFN (Hou *et al.* 2000). In a study among 327 carcinoid patients, those with a high titre of antibodies lost the response to treatment, but this phenomenon occurred late in the disease after a median of 25 months (Oberg & Alm 1997).

The second step in our treatment protocol was the administration of unlabelled MIBG, the cytotoxic effect of which is related to inhibition of mitochondrial respiration. In a previous series of 20 carcinoid patients, three cycles of unlabelled MIBG resulted in a good palliative effect in 60% (Taal *et al.* 1996). Apart from combining the two active treatment modalities, we hypothesised that IFN- α might induce differentiation of tumour cells, leading to facilitation of MIBG transport and uptake, and hence improved clinical results. This was based on the *in vitro* results of IFN- α in a neuroblastoma cell line (Montaldo *et al.* 1992). As differentiation might

occur with IFN- α as well after some time *in vivo* (Oberg 1992), we choose a period of 2 months of treatment with IFN- α .

A favourable effect upon biodistribution (> 10% increase) at the ¹³¹I-MIBG scintigraphy was seen in only 19% of the patients. Overall, IFN did not affect the MIBG uptake in carcinoid patients significantly. This might be explained by a different effect of IFN- α compared with IFN- γ as used in the cell-line model, or a different reaction of the carcinoid tumour cells compared with the neuroblastoma cells. Another explanation that the duration of treatment (8 weeks) might have been too short to induce cell differentiation seems unlikely. However, significant increase in biodistribution and tumour uptake was induced by unlabelled MIBG given directly prior to the ¹³¹I-MIBG scintigraphy in 83%.

The combination of MIBG and IFN was well tolerated, and in only one patient was a transient rise in

blood pressure seen as an adverse effect. Unfortunately, the addition of MIBG to IFN resulted in only one more response, leading to an overall response rate of 39%.

Quality of life measurements of the five functioning scales as well as global health showed no significant improvement. However, among the single-item scores, flushes and worries about disease progression improved significantly. The only other study dealing with quality of life evaluation in relation to treatment is by Wymenga *et al.* (1999), in which the somatostatin analogue lanreotide resulted in an early but temporary improvement of emotional and cognitive functioning, as well as the global health scale. As serotonin is involved in the aetiology of depression and depression is one of the possible side-effects of IFN, we also applied questionnaires to measure the symptoms of depression. However, clinically important depression was not seen before the start and did not develop during the treatment. These findings are in line with the report of 24 carcinoid patients in Sweden in whom a low level of anxiety and depression was found during a year of follow-up (Larsson *et al.* 2001).

To study the symptoms in a different manner, we also divided the patients into two groups based on the predominant symptoms. Twenty-nine percent of patients with the carcinoid syndrome mentioned an additional improvement with unlabelled MIBG, and 75% of cases of systemic symptoms such as fever, anorexia and fatigue. Compared with a 60% response rate as a single agent (Taal *et al.* 1996), the combination of unlabelled MIBG with IFN is probably not more effective.

The final step in the protocol consisted of radioactive MIBG as an adjunct to IFN treatment in cases of positive scintigraphy, to provide a local irradiation dose. In the present study, 14 patients received at least one cycle resulting in one PR. ^{131}I -MIBG has been shown to induce long-term palliative effect in 60% of patients with metastatic carcinoid tumours described earlier by our group (Taal *et al.* 1996, 2000). Mukherjee *et al.* (2001) reported similar favourable results with a subjective response in 11 out of 18 (73%) patients. In another study including several types of neuroendocrine tumours (Pathirana *et al.* 2001), a subjective response rate of 83% was reported in the subgroup of ten patients with carcinoid tumours, following only one cycle of ^{131}I -MIBG.

The side-effects of radioactive MIBG were not increased by the concomitant use of IFN and were still limited to nausea and vomiting in a small minority of patients.

The treatment with radiolabelled MIBG is only given to patients with a positive MIBG scintigraphy. To be able to select more patients for this treatment, we could improve results by pretreatment with unlabelled MIBG as

described earlier (Taal *et al.* 2000). In the present study, long-term pretreatment with IFN did not show such a favourable effect.

In conclusion, IFN- α results are comparable with those described in the literature. Although an increased uptake of ^{131}I -MIBG was seen in 19%, the increased clinical response rate to combined treatment with both unlabelled and ^{131}I -labelled MIBG was disappointing and restricted to patients with the carcinoid syndrome or other systemic symptoms.

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