Diagnostic and treatment modalities in carcinoid tumours

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Chapter 6

Interferon and MIBG combinations

in the treatment of metastatic carcinoid tumours

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Chapter 6

Abstract

Background: Interferon (IFN) and meta-iodobenzylguanidine (MIBG) are active in metastatic carcinoid. In a phase II study we evaluated the effect upon diagnostic $^{131}$I-MIBG uptake and the clinical response of the combination.

Methods: $^{131}$I-MIBG scintigraphy was performed prior to treatment, after 8 weeks of interferon 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).

Results: T/NT1 ratio showed an increase of >10% in only 4 out of 21 patients (19%) after IFN (p=0.178) and significantly more often in 9/18 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 showed 91% stable disease (using the WHO criteria) at CT-scan and biochemical response (a reduction of at least 50% in urinary 5-HIAA excretion) in 39%.

Conclusion: Interferon-α did not significantly improve tumour retention of $^{131}$I-MIBG. In contrast, unlabelled MIBG significantly improved biodistribution and tumour uptake in 83%. A synergistic effect was not seen.
Introduction

Carcinoid tumours are neuroendocrine tumours associated with the synthesis and secretion of biological active substances that can induce characteristic symptoms of the carcinoid syndrome (flushing, diarrhoea and wheezing). Metastatic disease at diagnosis is found in 22%, and largely dependent on the primary localisation: appendix 1.5%, lung 4.8% and small and large bowel localisations 28% (excluding appendix and rectum). Various treatment strategies have been recommended, mainly aimed at amelioration of the incapacitating symptoms. Surgery is indicated for the primary tumour in case of obstruction. In metastatic disease of the liver, palliative resection may be of value, but is usually not feasible due to diffuse involvement of both liver lobes. For medical treatment, somatostatin analogues and/or interferon-α (IFN) formulations are employed by many clinicians, as biochemical and subjective responses are observed in 70% and 80% respectively for somatostatin analogues, and 40% and 70% respectively for interferon-α formulations. Pharmacological doses of meta-iodobenzylguanidine (MIBG) resulted in symptomatic improvement in 60% of the carcinoid patients. The cytotoxic effect of MIBG is related with 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. Another possibility is treatment with radio-labelled 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 part of the patients. Worldwide experience with 131I-MIBG diagnostic imaging has indicated a cumulative sensitivity of 70% in 237 patients with carcinoid tumours. Predosing with unlabelled MIBG resulted in improved tumour targeting, biochemical response and hence prolonged palliation. Carcinoids are known to take up amino-acid precursors for the endogenous production of serotonin. Recent reports suggest a role of vesicular monoamine transporters (VMAT's) in this uptake. Pre-treatment with unlabelled MIBG can give 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 the pre-treatment with interferon-α. This assumption is based on the laboratory findings of an improved uptake of 125I-MIBG following interferon-γ administration in neuroblastoma cell lines. This phenomenon was based on de-novo synthesis of MIBG receptor transporters. Although interferon-α is different from interferon-γ, differentiation of carcinoid tumour cells with the application of interferon-α is described with good clinical results. It was hypothesized that the combination of two active treatment modalities (interferon and MIBG) may lead to an additive or even synergistic effect.

In the currently presented phase II study we examined the effect of interferon-α upon diagnostic 131I-MIBG uptake by carcinoid tumours, and whether the clinical response,
including quality of life, to interferon-α therapy was improved by MIBG. In addition interferon-α antibody formation was evaluated for influencing therapy results.

Patients and methods

Patients

Patients referred to our hospital between October 1996 and December 1998, with metastatic carcinoid tumours, a WHO performance status 0-2, normal blood cell counts and renal function were eligible. Twenty-six consecutive patients (18 men and 8 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 neuroendocrine tumour was confirmed by histology. In 2 patients fine needle aspiration led to the diagnosis; one patient refused a biopsy and the diagnosis was based on strongly elevated 5-hydroxyindoleacetic acid (5-HIAA) excretion and symptoms. Three patients had normal urinary 5-HIAA excretions; median pre-treatment urinary 5-HIAA excretion in the 23 secretors was 503 μmol/24h (normal < 40 μmol/24h). Twenty-two patients (85%) suffered from the carcinoid syndrome with diarrhoea and/or flushes at the time of enrollment. Fifteen patients had complaints, related to tumour size or localisation. Median duration of symptoms before start of treatment was 7 months (range: 0-94 months). In 11 patients the indication for enrollment was progression under systemic therapy and in two after prior surgery; the remaining patients were not pre-treated. 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 interferon-α 2a (Roferon®), 6 million IU thrice weekly s.c. After 8 weeks, unlabelled MIBG was added in three cycles of increasing doses (10, 20 and 40 mg/m$^2$) in a 4-hour infusion every 4 weeks as described earlier. Subsequently, patients with a positive $^{131}$I-MIBG scan received two therapeutic doses of (7.4 GBq) $^{131}$I-MIBG administered during a hospital stay. IFN-α 2a therapy was continued for 6 months, and only stopped if serious side effects persisted, or in case of progressive disease. During this study, ten patients were treated with somatostatin analogues which was continued in a stable dosage.
Methods

The effect of interferon-α upon $^{131}\text{I}$-MIBG tumour uptake was evaluated by comparing $^{131}\text{I}$-MIBG scans prior to and after 8 weeks treatment. Subsequently, the effect of unlabelled MIBG was evaluated by the $^{131}\text{I}$-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.\textsuperscript{18} In case of extra hepatic tumour localisation the T/NT3 ratio was calculated by comparing this particular localisation with the abdominal background. A 10% increase in biodistribution was considered a clinical important difference.

CT-scans were performed before start, after 8 weeks of interferon treatment, after the third course of unlabelled MIBG and after the last course of $^{131}\text{I}$-MIBG. CT-scans were systematically reviewed without the 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 (CR): 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 (CTC).

IFN-α 2a antibody concentrations before and after at least 4 months of IFN therapy were analysed using an enzyme immuno assay (EIA) method.\textsuperscript{19} An antibody titre rise was considered significant if the post-IFN value exceeded the 95\textsuperscript{th} 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.\textsuperscript{20,21} Questions were added to evaluate the specific carcinoid symptoms such as flushes and abdominal cramps and the specific side effects of interferon such as chills and muscle pain. All scores were linearly converted to a 0 to 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 CES-D (Center for Epidemiologic Studies depression scale) list of 20 items was included to measure depression.\textsuperscript{22} A score of 16 or more indicated depression.\textsuperscript{23,24} 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 improved if the patient experienced a
clear reduction (e.g. weight gain or >50% less additional medication) or disappearance in symptoms, and progression in case of deterioration. Survival and time to progression (TTP) were measured from start of treatment. TTP was defined as the number of months between start of IFN and a change in therapeutic regimen because of progression.

Statistics
For statistical analysis the two-sided, paired T-test was applied with a p-value of 0.05 as 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 was used.

Table 1. Clinical characteristics of patients

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</tr>
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</tr>
<tr>
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<tr>
<td>Female</td>
<td>8</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
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<tr>
<td>Primary site</td>
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<tr>
<td>Lung</td>
<td>5</td>
</tr>
<tr>
<td>Stomach</td>
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</tr>
<tr>
<td>Unknown</td>
<td>14</td>
</tr>
<tr>
<td>Therapy (number of patients)</td>
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</tr>
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<td>Somatostatin analogues</td>
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<td>Interferon-α 2a</td>
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</tr>
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<td>MIBG (&gt; 2.5 years before study)</td>
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</tr>
<tr>
<td>111I-MIBG (&gt; 2.5 years before study)</td>
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<td>Chemotherapy</td>
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<td>Radiotherapy (skin metastases)</td>
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<td>Duration of symptoms before start study (months)</td>
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<tr>
<td>Median (range)</td>
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<td>Predominant symptoms</td>
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<td>Carcinoid syndrome</td>
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<td>Abdominal pain (unrelated to carcinoïd syndrome)</td>
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<td>None</td>
<td>1</td>
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<td>Progression under therapy</td>
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<td>Urinary 5-HIAA excretion (µmol/24h) at start study</td>
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<tr>
<td>&lt;ULN (n=3) median (range)</td>
<td>23 (21-34)</td>
</tr>
<tr>
<td>&gt;ULN (n=23) median (range)</td>
<td>503 (130-3131)</td>
</tr>
</tbody>
</table>

MIBG: meta-iodobenzylguanidine
5-HIAA: urinary 5-hydroxyindoleacetic acid (normal < 40µmol/24h)
ULN: upper limit of normal
Results

Protocol evaluation
Twenty-three patients completed the first 8 weeks of IFN therapy. Three patients stopped within 8 weeks due to 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 gift of MIBG. In one patient the third treatment with MIBG was not administered as the previous two failed to reach symptom relief.

Among the twenty patients who reached week 21, seven patients received 2 cycles of 7.4 GBq $^{131}$I-MIBG and fully completed the protocol. Seven patients received only one cycle of $^{131}$I-MIBG: two patients due to progressive disease, two patients based on thrombocytopenia, one patient pre-treated with $^{131}$I-MIBG reached his cumulative maximal radiation dose, and in two patients a temporary drop in WHO performance status prevented further $^{131}$I-MIBG infusion. Six patients were not given $^{131}$I-MIBG as their $^{131}$I-MIBG scan was negative, but they continued interferon-$\alpha$ as planned.

Responses, time to progression, survival, 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 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 3 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 2 courses of $^{131}$I-MIBG, 2/20 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, 17/26 (65%) patients had SD.

Biochemical evaluation with urinary 5-HIAA excretion: after 8 weeks of IFN therapy, in 8 out of 23 (35%) patients with elevated urinary 5-HIAA values a PR was reached. At 21 weeks, one additional patient reached a PR, who previously showed SD. The protocol resulted in an overall best response rate (according to the 5-HIAA excretion) of 39%.

The tumour over normal liver tissue T/NT1 ratio of the $^{131}$I-MIBG retention showed a 10% increase in only 4 out of 21 patients (19%) after interferon treatment, while this was the case in 9/18 patients (50%) after unlabelled MIBG (Table 2). Using the tumour over abdominal background ratio (T/NT2) these figures were even more pronounced: 23% after interferon and 83% after unlabelled MIBG (Figure 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 7 patients and the T/NT3 ratio showed similar effect after interferon and MIBG with 23% and 83% respectively. Overall, the changes after interferon treatment were not statistically significant (p=0.178). In contrast, after treatment with unlabelled MIBG a significant (p=0.016) increase was found.

**Figure 1.** $^{131}$I-MIBG scintigraphy before (pre-interferon) and after (post-interferon) treatment with interferon (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 respectively 7% and 3%. After application of unlabelled MIBG, uptake in both localisation was increased by 31% and 69% respectively.

<table>
<thead>
<tr>
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<th>Pre-interferon</th>
<th>Post-interferon</th>
<th>after cold MIBG</th>
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<tbody>
<tr>
<td>anterior</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>T/NT liver</td>
<td>1.46, lung 3.43</td>
<td>1.56, lung 3.54</td>
<td>2.05, lung 5.99</td>
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<tr>
<td>posterior</td>
<td></td>
<td></td>
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</table>

124
<table>
<thead>
<tr>
<th></th>
<th>T/NT1 ratio</th>
<th>T/NT2 ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(tumour over normal liver tissue ratio)</td>
<td>(tumour over abdominal background ratio)</td>
</tr>
<tr>
<td>&gt;10% increase in $^{131}$I-MIBG uptake</td>
<td>After IFN treatment: 4/21 (19%)</td>
<td>After IFN treatment: 5/21 (23%)</td>
</tr>
<tr>
<td></td>
<td>After MIBG application: 9/18 (50%)</td>
<td>After MIBG application: 15/18 (83%)</td>
</tr>
<tr>
<td>No change in $^{131}$I-MIBG uptake</td>
<td>After IFN treatment: 16/21 (76%)</td>
<td>After IFN treatment: 10/21 (48%)</td>
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<tr>
<td></td>
<td>After MIBG application: 7/18 (39%)</td>
<td>After MIBG application: 3/18 (17%)</td>
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<tr>
<td>&gt;10% decrease in $^{131}$I-MIBG uptake</td>
<td>After IFN treatment: 1/21 (5%)</td>
<td>After IFN treatment: 6/21 (29%)</td>
</tr>
<tr>
<td></td>
<td>After MIBG application: 2/18 (11%)</td>
<td>After MIBG application: 0/18 (0%)</td>
</tr>
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</table>

IFN: Interferon
MIBG: meta-iodobenzylguanidine
The median time to progression (TTP) was 9 months and after 18 months 90% of the patients had progressive disease. Median overall survival (Figure 2) from the start of the present treatment protocol was 27 months, while the five-year survival was 33%. In patients with an increased tumour retention at $^{131}$I-MIBG scintigraphy after interferon, survival was comparable ($p=0.89$) to the others (median 32 vs. 38 months). Neither 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 pre-treated patients survival tended ($p=0.20$) to be shorter compared with not-pre-treated cases (18 vs. 37 months).

Interferon 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.

**Figure 2.** Survival and time to progression (TTP). Median time to progression was 9 months, median survival was 27 months with a five-year survival of 33%. Eight patients were still alive during last follow-up
Antibodies against recombinant human IFN-α 2a and time to progression

A second blood sample used for IFN-α antibody titre determination, taken 4-6 months after the start of the interferon 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 the disease duration at the start of the protocol were not significantly different between patients with and without development of antibodies. A difference in response and time to progression was not found, but overall survival (Figure 3) was significantly better in patients without antibody formation (p=0.04).

Figure 3. Time to progression according to the development of an IFN-α 2a titre rise after at least 3 months of IFN-α 2a treatment. In 6/19 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)

No rise in anti-body titre against IFN-α 2a after >3months IFN treatment (n=13).

Rise in anti-body titre against IFN-α 2a after >3months IFN treatment (n=6).

Survival

Months after start

p= 0.04
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<th>Functioning scales</th>
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<th>SD</th>
<th>T0-T8 Mean</th>
<th>SD</th>
<th>P</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>T8-T21 Mean</th>
<th>SD</th>
<th>P</th>
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<tr>
<td>Physical Functioning</td>
<td>20</td>
<td>79.3</td>
<td>17.3</td>
<td>-2.0</td>
<td>17.7</td>
<td>.619</td>
<td>18</td>
<td>80.6</td>
<td>18.2</td>
<td>-3.1</td>
<td>12.2</td>
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<td>27.8</td>
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<td>18</td>
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<td>-1.9</td>
<td>26.1</td>
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<td>20.4</td>
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<td>18</td>
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<td>18</td>
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<td>18</td>
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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.
Symptoms, Quality of life and depression

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

By comparing patients with predominantly carcinoid symptoms (n=14) with patients complaining from other systemic symptoms like 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 interferon compared with 4/14 (29%) following unlabelled MIBG (p=0.3). Similarly, 3/8 (38%) patients with systemic symptoms mentioned improvement by interferon, but they did better after unlabelled MIBG with a response in 6/8 (75%) (p=0.14). Overall, after MIBG treatment patients with systemic symptoms responded significantly better on MIBG treatment compared with patients with carcinoid syndrome (p=0.04).

Discussion

Interferon-α formulations are well known for their therapeutic effect in metastatic carcinoid disease: subjective responses can be achieved in up to 70% of patients, biochemical responses are observed in 40-50%. A measurable tumour reduction, however, is only occasionally reported. The anti-proliferative effect of interferon-α has, at least in part, been ascribed to a delay in the S-G2/M phase transit. In line with the literature, the present study showed a biochemical response rate of 35% with interferon-α 2a monotherapy, 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 well responsive to paracetamol.

In 32% of our patients neutralizing antibodies were detected during follow-up. The response to the treatment protocol and the time to progression 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 interferon administration, at least in patients with hepatitis B. This was confirmed in a more recent paper of patients with hepatitis C treated with interferon. 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.

The second step in our treatment protocol was the administration of unlabelled MIBG, which cytotoxic effect is related to inhibition of mitochondrial respiration. In a prior series
of 20 carcinoid patients, 3 cycles of unlabelled MIBG resulted in a good palliative effect in 60%. Apart from combining two active treatment modalities, we hypothesized that interferon-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 interferon-γ in a neuroblastoma cell-line. As differentiation might occur with interferon-α as well after some time in vivo, we choose a period of two months treatment of interferon-α.

A favourable effect upon biodistribution (>10% increase) at the 131I-MIBG scintigraphy was seen in only 19% of the patients. Overall, interferon did not affect significantly the MIBG uptake in carcinoid patients. This might be explained by a different effect of interferon-α compared with interferon-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) to induce cell differentiation might have been to short, 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 interferon was well tolerated, and in only one patient a transient rise in blood pressure was seen as an adverse effect. Unfortunately, the addition of MIBG to interferon 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 the paper of Wymenga et al., 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 symptoms of depression. However, clinically important depression was not seen before start and did not develop during the treatment. These findings are in line with the report among 24 carcinoid patients in Sweden in whom a low level of anxiety and depression was found during a year of follow-up.

To study the symptoms in a different manner we also divided the patients in two groups based on the predominant symptoms. Patients with the carcinoid syndrome mentioned an additional improvement by unlabelled MIBG in 29%, and in case of systemic symptoms such as fever, anorexia and fatigue in 75%. Compared with a 60% response rate as a single agent, the combination of unlabelled MIBG with interferon is probably not more effective.

The final step in the protocol consisted of radioactive MIBG as an adjunct to interferon treatment in case of a 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.\textsuperscript{6,11} Mukherjee et al. reported similar favourable results with a subjective response in 11 of 18 (73%) patients.\textsuperscript{10} In another study including several types of neuroendocrine tumours\textsuperscript{9}, a subjective response rate of 83% was reported in the subgroup of 10 patients with carcinoid tumours, following only one cycle of $^{131}$I-MIBG.

Side effects of the radioactive MIBG were not increased by the concomitant use of interferon 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 pre-treatment with unlabelled MIBG as described earlier.\textsuperscript{11} In the present study long-term pre-treatment of interferon did not show such a favourable effect.

In conclusion, interferon-α results are comparable to 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.
Chapter 6

References


