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LONG-TERM MANAGEMENT OF THE CARCINOID SYNDROME

Treatment with octreotide alone and in combination with alpha-interferon

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Fifty-five patients with metastatic carcinoid tumor were treated with the long-acting somatostatin analogue octreotide. Nineteen received in addition alpha-interferon when octreotide had failed. During octreotide treatment reduced flush and/or diarrhea was seen in 70% of the patients, 37% showed >50% decrease in urinary 5-HIAA for a median of 8 months. A further 49% experienced stabilization of their disease and only 14% progressed. One patient showed reduced tumor size. Of the 19 patients given alpha-interferon in combination with octreotide, 72% showed significant reduction in urinary 5-HIAA for a median of 10 months. Twenty-two percent became stabilized and only 6% progressed. A symptomatic improvement was seen in 49%. The combination was well tolerated. Our data confirm previous studies, showing that octreotide is useful for treatment of the carcinoid syndrome. Our results also indicate that the combination of octreotide and alpha-interferon might be of beneficial value for long-term management of this disease.

Carcinoid tumors are the most common neuroendocrine tumors of the gastrointestinal tract with an estimated incidence of 2.1/100 000 people. They are divided into fore-gut, mid-gut and hind-gut tumors depending on the localization of the primary tumor (1). These tumors demonstrate a rather low proliferation rate and are highly differentiated with a capacity to produce various hormones, e.g. tachykinins, bradykinins and serotonin. The most useful biochemical marker for therapy monitoring has been the urine serotonin metabolite, 5-hydroxyindoleacetic acid (urinary 5-HIAA) (2). After development of liver metastases, the mid-gut carcinoid tumors give rise to the carcinoid syndrome (3). This syndrome includes flushing, diarrhea, bronchial constriction and the carcinoid heart disease due to secretion of substances from the tumors (4, 5).

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The clinical management of this syndrome, which sometimes can exhibit life-threatening symptoms, such as severe bronchial constriction, hypotension and profuse diarrhea with dehydration, is important. Furthermore, one-third of the patients might die from right-side heart complications related to substances released from the carcinoid tumors (6). The 5-year life expectancy is only 8–21% untreated (7).

Chemotherapy has not been of any benefit to most of these patients. Objective response rates of 10–30% have been noted for the most used combinations with streptozocin and 5-fluorouracil or doxorubicin while the adverse reactions have been considerable (8–10).

Somatostatin, a tetradecapeptide, purified from hypothalamic tissue (11) has the potential to inhibit the secretion of numerous hormones, not only from the gastrointestinal tract (12). It also reduces splanchnic blood flow and inhibits motility of the biliary ducts. The ability to inhibit hormone release made this molecule highly interesting as a possible blocking agent for the carcinoid syndrome, and indeed continuous infusion of somatostatin has been tried with promising results (13, 14). But since natural somatostatin has a short half-life in plasma, it was not until a long-acting somatostatin analogue, octreotide, was developed (15) that it came into a wider clinical use.

In 1986, Kvols et al. reported on a material including 25 patients with metastatic carcinoid disease receiving octreotide treatment lasting up to 18 months, with a significant reduction of U-5HIAA in 72% of patients (16). Others have reported similar results (17, 18).

Alpha-interferon, a member of the cytokine network, has been used in cancer treatment for some years. It has many different modes of action, such as immune stimulating and induction of mRNA for 2'5'A-synthetase, p 68 kinase and Mx-protein. It also has a direct growth inhibiting activity on tumor cells including down-regulation of growth factors and receptors as well as oncogene expression and cell-cycle blockage (19). In previous studies on malignant carcinoid tumors it has proven to be useful in the long-term management of patients suffering from the carcinoid syndrome, since it reduces symptoms as well as tumor markers and tumor growth. A biochemical response with >50% reduction in U-5HIAA has been seen in about 39–50% of the patients lasting for almost 3 years in one study (20–22).

Since carcinoid tumors advance rather slowly, treatment may have to be continued for many years and neither octreotide nor alpha-interferon cures the patients. We have therefore combined these two drugs in order to obtain more long-lasting results, and to see whether resistance to octreotide at the same time means lack of response to alpha-interferon. Furthermore, since both somatostatin analogues and alpha-interferon demonstrate anti-mitogen activity (19, 23) a combination might give significant reduction of tumor size and not only decreased hormone levels and symptoms.

Material and Methods

Altogether 55 patients were treated with octreotide. All had histologically verified carcinoid tumors, 43 had mid-gut carcinoid tumors while one had a lung carcinoid tumor (Table 1). In 11 patients the localization of the primary tumor was unknown, but the histological and immunohistochemical examination of liver biopsies from metastases indicated a mid-gut off-spring. All patients had metastatic disease confirmed either by CT or abdominal ultrasound investigations. The median urinary 5-HIAA at start of therapy was 450 μM/24 h ranging from 39 to 3 299 (ref. range 10–80 μM/24 h).

Fifty-one patients (95%) had a carcinoid syndrome with flush (n = 46) and/or diarrhea (n = 45), and those patients were evaluated for symptomatic response. Median duration from diagnosis until start of octreotide treatment was 21 months with a range of 0–316 months. Sixteen patients were previously untreated, 37 patients had received alpha-interferon and 17 patients chemotherapy (streptozotocin and 5-FU). The previous therapy was withdrawn 1–3 months prior to the start of octreotide treatment in all patients.

Table 1

Patient data

No. of patients	55
Females/males	28/27
Median age	67 years (38–82)
Median duration of disease prior to start of treatment	21 months (0–316)
Localization of primary tumor	43 mid-gut 1 fore-gut 11 unlocalized
Metastases	55/55 52 liver metastases 29 lymph node metastases
Increased U-5HIAA	50/55
Median U-5HIAA	450 μmol/24h (39–3299)
Carcinoid syndrome	51/55 46 flushes 45 diarrhea

Patients were monitored every third month for routine hemathology, liver and kidney function, blood glucose, serum electrolytes and urinary 5-HIAA, which was determined according to a method earlier described (24) and calculated as a mean of two 24-h urine collections. Tumor size was monitored by CT and ultrasound investigations every third month. A complete biochemical response was defined as a normalization of U-5HIAA, while partial biochemical response was considered to have occurred when U-5HIAA was reduced by 50% or more. An increase in U-5HIAA of 25% or more was regarded as tumor progression. A reduction of tumor size by more than 50%, calculated as the product of two perpendicular diameters of the two largest metastases, was considered a partial response while an increase by more than 25% was designated progression. The duration of response was calculated from start of treatment until the patient demonstrated >25% increase in U-5HIAA and/or tumor size or developed new metastases.

Results

The therapeutic results are summarized in Table 2.

At the start of octreotide therapy 49 patients had increased urinary 5-HIAA and one patient developed increased levels during treatment. Four patients died before biochemical response was evaluable, one was operated upon and two patients discontinued the treatment due to side-effects before biochemical evaluation. Thus 43 patients could be evaluated for biochemical response.

The most common starting dose of octreotide was 50 μg b.i.d. (n = 41), but doses up to 450 μg daily have been used initially. The median dose during follow-up was 100 μg b.i.d. (range 100–1 200), and the median duration of therapy was 14 months (1–58).

During treatment with octreotide alone, urinary 5-HIAA became normalized in 4 patients out of 43 evaluable

Table 2

Biochemical responses to treatment in patients with increased hormone levels

Treatment		OR%	SD%	PD%	Median duration of response
Octreotide	(n = 43)	37	49	14	8 months
Octreotide + alpha-interferon	(n = 18)	72	22	6	10 months

OR: objective response, SD: stable disease, PD: progressive disease

(9%) and another 12 patients (28%) showed a partial response. Thus, a total biochemical response of 37% was obtained with a median duration of 8 months and range of 2–48 months. One patient has shown a complete biochemical response for 46 months and is still in very good clinical condition. The tumor size decreased significantly in only one patient. Thirty-two of the 46 patients (70%) who reported flushes at the start of octreotide treatment experienced an improvement, whereas 31 of the 45 patients (69%) with diarrhea before treatment reported a reduction of this symptom. In 35 patients development of 'tachyfylaxia' with return of symptoms of the carcinoid syndrome occurred, and a dose escalation was necessary after a median time of 3 months. Dose escalation was performed more than once in 20 patients, and up to 4 times in single patients.

Nineteen patients, finally resistant to further dose escalation of octreotide, received alpha-interferon at doses individually titrated (2–6 MU × III-VII) as an addition to octreotide treatment. Of these 19 patients, 18 could be evaluated for biochemical response, since one patient had normal biochemical markers from the start. Four patients (22%) showed a normalization of urinary 5-HIAA and 9 (50%) a partial response, giving a total biochemical response of 72%. The median duration of this biochemical response was 10 months (range 2–31 months). Five of these 13 responding patients (38%) had previously demonstrated an objective response to octreotide alone, but relapsed and had not improved after dose escalation. Five patients demonstrated stable disease whereas one patient progressed and died after 6 months. A symptomatic improvement was noted in 9 out of 19 (47%) when alpha-interferon was added. None obtained a significant reduction in tumor size, while tumor size increased in 4 patients.

Adverse reactions due to octreotide therapy included malabsorbtive diarrhea and borborhygmia. These problems were usually managed by substitution with pancreatic enzymes. Four patients developed bilary stones during treatment and of these two patients presented cholangitis. A suspected allergic reaction was seen in one patient and a significant bradycardia in one. The majority of the patients reported slight pain at the injection site (Table 3).

In the group of patients treated with alpha-interferon, adverse reactions included flu-like symptoms during the initial 3–5 days of interferon treatment. Tiredness and muscle pain was a common complaint, and dose reduction was performed in 6 patients. Seven patients complained of anorexia and/or weight loss and in three patients alpha-interferon was withdrawn, but due to increasing urinary 5-HIAA levels reintroduced at lower doses without severe side-effects. One patient showed an allergic reaction during alpha-interferon treatment and one patient developed autoimmune vasculitis. In these two patients treatment was permanently withdrawn (Table 3).

Table 3

Adverse reactions

To octreotide	
Malabsorbtive diarrhea	17%
Borborhygmia	23%
Biliary stones	7%
Cholangitis	4%
Allergic reaction	2%
Bradycardia	2%
To interferon	
Flu-like symptoms	74%
Tiredness, muscle pain	53%
Anorexia, weight loss	37%
Allergic reaction	5%
Autoimmune vasculitis	5%

Twelve patients (22%) died during the octreotide treatment period after a median of 9 months range 1–40. Causes of death were tumor progression in 5 cases, pulmonary embolism, myocardial infarction and right heart failure in one case each and unknown in 4 patients.

Discussion

The carcinoid syndrome has presented a therapeutic challenge over the years. Patients with this syndrome have been treated with different drug regimens when surgery has failed. Since the tumor itself is slowly advancing, both positive and negative effects of the treatment have to be balanced. Chemotherapy, with short-lasting objective responses in 10–30% of the patients accompanied by quite severe side-effects has not been of any beneficial value (8–10). Alpha-interferons have, for the last few years, also

been used with response rates of about 39–50% (20–22), lasting for almost 3 years in one study, and with tolerable side-effects. However, some patients do not respond to alpha-interferons, and the clinical and biochemical responses are not always immediate.

Somatostatin has been shown to block the release and peripheral action of different hormones (12). The long-acting analog octreotide has provided a clinical useful therapeutic agent with biochemical responses in up to 72% of patients (16). In our material, 70% of the patients experienced a relief of symptoms, usually during the first week of treatment. In 37% of our patients an objective biochemical response was observed. This response rate is somewhat less than previously reported (16) but might be due to differences in the patient material, such as stages of disease when therapy was started, e.g. the median age in our material is 9 years higher than that in the Mayo Clinic study (16) which might indicate a more advanced disease.

Development of tachyfylaxia was noted in 35 of our patients after a median of 3 months. This is one of the major problems during long-term treatment with octreotide (25). The etiology of the tachyfylaxia is not yet elucidated, but might include down regulation of somatostatin receptors as well as changes in intracellular signal transduction (26).

When combining alpha-interferon and octreotide, an objective biochemical response rate of 72% lasting for 10 months was seen, indicating at least an additive effect of alpha-interferon. Furthermore there does not seem to be any 'cross-resistance' between the two drugs. Thus, by adding alpha-interferon the carcinoid disease could be controlled for almost one additional year.

The adverse reactions noted to octreotide were few and quite easy to manage. All patients received substitution with pancreatic enzymes from the start of octreotide therapy, to reduce malabsorbtive diarrhea. This might explain the low frequency of steatorrhea. Development of bilary stones and cholangitis were more severe to manage, and we would not recommend long-term treatment in patients with a history of biliary dysfunction.

Alpha-interferon might cause more severe adverse reactions and might not be as well tolerated as octreotide, but there is no additive or synergistic toxicity and therefore the patients tolerated the combination quite well.

In conclusion, both octreotide and alpha-interferon are important contributors to the therapeutic arsenal for symptomatic amelioration of the carcinoid syndrome. The combination of both drugs demonstrate additive clinical effects without any severe toxicity. There does not seem to be any 'cross-resistance' between the two drugs. The combination of octreotide and low dose alpha-interferon seems to be of beneficial value for long-term management of patients with malignant carcinoid tumors and the carcinoid syndrome.

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