Interferons in the Management of Neuroendocrine Tumors and Their Possible Mechanism of Action

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Received May 11, 1992

Alpha interferons at doses of 3–9 MU subcutaneously, three to seven times/week, have been administered to 32 patients with malignant endocrine pancreatic tumors. The objective biochemical response rate was 63 percent with a median duration of 20.5 months. Significant reduction of tumor size was only noticed in 20 percent of the patients. Alpha interferon administered to 111 patients with malignant carcinoid tumors showed objective biochemical responses in 42 percent of the patients with a median duration of 32 months. Another 39 percent of the patients showed stabilization of disease without any further tumor growth. Subjective improvement was noticed in 70 percent of the patients. When survival data are analyzed in patients with malignant carcinoid tumors, the median survival from start of treatment was 80+ months in the group of patients treated with alpha interferon, which should be compared with only eight months in a historical group treated with chemotherapy (streptozotocin plus 5-fluorouracil). The adverse reactions to alpha-interferon treatment are dose-dependent and include, mainly, flu-like symptoms, fatigue, and low-grade weight loss. Autoimmune reactions are noted in about 20 percent of the patients. Patients treated with recombinant alpha interferons might develop neutralizing interferon antibodies (6–27 percent), which abrogate the anti-tumor response.

The anti-tumor effect in neuroendocrine tumors includes anti-proliferation, apoptosis, differentiations, and cytotoxic/cytostatic effects. Furthermore, immunomodulation is obtained by increased expression of class I antigens on tumor cells. Four patients also developed antibodies directed against carcinoid tumor cells. Alpha interferons induce several nuclear enzymes such as 2'-5'-A synthetase, p-68 kinase, and Mx-A proteins, which are involved in a downregulation of expression of growth factors, oncogenes, and peptide hormones, leading to anti-proliferation and/or apoptosis. The response to alpha-interferon treatment might be predicted by analysis of the induction of 2'-5A synthetase in samples from neuroendocrine tumors. Stimulatory tests of hormone secretion, such as meal stimulation of pancreatic polypeptide secretion or secretin test, clearly demonstrate a normalization during alpha-interferon treatment, which might depend on reduced peptide production and/or secretion but also on eradication of malignant cell clones.

In summary, alpha interferons have demonstrated significant anti-tumor effects in patients with malignant neuroendocrine gut and pancreatic tumors. The adverse reactions are dose-dependent and manageable. The anti-tumor effects of alpha interferons are pleiotropic and include several direct effects on tumor cells but also immunomodulation.

INTRODUCTION

Neuroendocrine gut and pancreatic tumors constitute about 2 percent of all malignant neoplasms annually diagnosed in the Western world. The incidence of

Abbreviations: APUD: amine precursor uptake and decarboxylation  5-HIAA: 5-hydroxyindole acetic acid IFN: interferon ISGF-3: interferon-sensitive growth factor 3 ISRE: interferon-sensitive response element(s) NPK: neuropeptide K PET: positron emission tomography

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patients with malignant tumors and the carcinoid syndrome is about 0.5 per 100,000
and with endocrine pancreatic tumors 0.4 per 100,000 [1,2]. The tumors, even in
advanced stages with metastases, demonstrate high degrees of differentiation, with
primarily diploid DNA features. A majority of patients with malignant metastasizing
tumors demonstrate clinical symptoms related to hormone overproduction. These
syndromes include the carcinoid syndrome with flushing, diarrhea, bronchial constric-
tion, and right heart failure due to classical mid-gut carcinoids with production of
serotonin and tachykinins. Other syndromes related to endocrine pancreatic tumors
are the Zollinger-Ellison syndrome, due to gastrin overproduction, insulinoma, or
hypoglycemic syndrome because of insulin/proinsulin overproduction. Other distinct
clinical entities are the glucagonoma syndrome, including the typical necrolytic
migratory erythema because of glucagon production, the Verner-Morrison syndrome
because of high circulating levels of VIP giving severe secretory diarrhea with various
degrees of electrolyte disturbances, and, finally, somatostatinoma syndrome with gall
bladder dysfunction, gallstones, steatorrhea, and impaired glucose tolerance.

About one-third of the patients present endocrine tumors of the pancreas without
any hormone-related clinical syndromes [2], and, in addition, neuroendocrine tu-
mors of the hind-gut area also often do not present any peptide hormone-related
syndromes [3]. The hormone production by itself, with related metabolic conse-
quences, might sometimes be life-threatening, even in patients with rather small
tumors and a limited number of metastases. About one-third of patients with the
carcinoid syndrome die from a carcinoid heart disease and not from tumor growth
[1]. Therefore, even if the tumor itself is advancing slowly, the hormone overproduc-
tion might be very harmful to the patient, producing a reduced quality of life.

Because of these tumors' rarity, sometimes episodic expression, and diffuse
clinical symptoms, patients are diagnosed rather late in advanced stages of the
disease. Therefore, surgery, although the treatment of choice, is rarely curative, and
medical treatment is necessary. Neuroendocrine gut and pancreatic tumors have
been assigned a good prognosis, and, therefore, many physicians have been reluctant
to administer medical treatment in early stages of the disease. A critical look at
five-year survival rates in patients with malignant neuroendocrine tumors, however,
demonstrates survival rates that are less than 20 percent when liver metastases are
present. The median survival for patients with malignant carcinoid tumors and the
carcinoid syndrome is less than two years from diagnosis of a carcinoid syndrome
[4,5].

Medical Treatment

The medical treatment of neuroendocrine gut and pancreatic tumors includes
chemotherapy, somatostatin analogs, and interferons. Monoclonal antibodies might
be a new therapeutic modality in the future. Chemotherapy has been used for at least
three decades, and several single agents as well as combined treatment modalities
have been applied. So far, a combination of streptozotocin and 5-fluorouracil or
adriamycin has been the most successful, giving biochemical response rates of about
60 percent in patients with endocrine pancreatic tumors but only 10–30 percent in
patients with carcinoid tumors and malignant carcinoid syndrome [6–9]. Native
somatostatin has been tried since the late 1970s, but, because of its short half-life in
plasma, treatment is restricted. During the 1980s, development of somatostatin
analog made this treatment clinically feasible, and it was possible to introduce
subcutaneous treatment with two or three administrations per day. There are studies of both endocrine pancreatic tumors and carcinoids which have demonstrated biochemical response rates of about 32–75 percent [10–12]. Whether the somatostatin analog could demonstrate an anti-proliferative effect with reduction of tumor size has been debated over the years, but there is increasing evidence that high-dose treatment, around 3,000 µg/day, might induce significant tumor reductions in a number of patients with malignant neuroendocrine tumors [13]. This high-dose treatment is currently being explored in studies in Europe and the U.S.

**Interferon Therapy**

Alpha interferon (IFN) was introduced by our group in the treatment of carcinoid tumors in 1982 because of its ability to control hormone secretion, clinical symptoms, and tumor growth [14]. Since then, more than 200 patients have been treated with alpha interferons at various dosages, and the largest studies are summarized in Table 1 [15–25]. The largest series of patients with endocrine pancreatic tumors has been treated at our institution (including 32 patients with various clinical syndromes) [23]. The dose of alpha interferon was 3–9 MU subcutaneously three to seven times per week, with a median of 6 MU five times per week. The objective biochemical response rate (>50 percent reduction of principal tumor markers) was 63 percent with a median duration of 20.5 months. Significant reduction of tumor size (>50 percent reduction of the product of two perpendicular diameters) was noticed in 20 percent of the patients.

A significant number of patients with carcinoid tumors and malignant carcinoid syndrome have been treated with alpha interferon at various doses (refer to Table 1). At our own institution, alpha interferon was administered to 111 patients with malignant carcinoid tumors and liver metastases [16]. We obtained biochemical responses in 42 percent of the patients, with a median duration of 32 months. Another 39 percent of the patients showed stabilization of their disease without any further tumor growth. Sixteen percent of the patients demonstrated significant reduction of tumor size, whereas 70 percent experienced a subjective improvement. Survival data on our patients with malignant carcinoid tumors were analyzed. The median survival from start of treatment was 80+ months in the group of patients treated with alpha interferon, which is tenfold longer than that of a historical group at our own institution, treated with chemotherapy (streptozotocin plus 5-fluorouracil), reaching a median survival of only eight months. This historical study has still to be evaluated in a randomized controlled study.

As indicated in Table 1, the biochemical response rates in various studies are about 42 percent with a tumor response median of 11 percent. Moertel and colleagues [15] administered a very high dose of recombinant interferon alpha 2a (median, 48 MU every second day), which did not increase the response rates of either biochemical responses or tumor responses. They could not continue with this treatment for longer periods than a median of eight weeks. In most other studies, low to medium doses have been applied with a median of about 5 MU three to five times per day, subcutaneously. The tolerance curve for alpha interferon seems to be bell-shaped, and, therefore, it is very important to titrate individual doses for each patient for long-term management. At our institution, we have empirically been using the leukocyte count as an indicator of anti-proliferative effects of alpha interferon, aiming at reducing the leukocytes below $3.0 \times 10^9/l$. Using this method,
| Study [Reference]       | Number of Patients | Dose                                        | Biochemical Response (%) | Tumor Response (%) |
|------------------------|--------------------|---------------------------------------------|--------------------------|--------------------|
| Moertel CG, et al., 1989 [15] | 27                 | IFN-2a 24 MU/m² × 3/w s.c.                  | 39                       | 20                 |
| Schober C, et al., 1989 [24]       | 21                 | IFN-2b 3 MU/m² × 3/w s.c.                  | 56                       | 10                 |
| Hanssen LE, et al., 1989 [18]      | 19                 | IFN-2b 5 MU × VIII/w s.c.                  | 40; 86                   | 10; 86             |
|                         |                    | alone* or with embolization                |                          |                    |
| Bartsch HH, et al., 1990 [19]      | 18                 | rIFN-2c 2 MU/m² × XII/w s.c.               | 44                       | 0                  |
| Välimäki M, et al., 1991 [20]      | 8                  | nIFN-α 3 MU × VII/w s.c.                  | 50                       | 12.5               |
| Öberg K, et al., 1986 [21]         | 37                 | nIFN-α 6 MU × VII/w i.m.                  | 49                       | 11                 |
| Öberg K, et al., 1989 [22]         | 21                 | rIFN-2b 5 MU × III/w s.c.                 | 53                       | 0                  |
| Norheim I, et al., 1989 [17]       | 20                 | nIFN-α 6 MU × VII/w s.c.                  | 50                       | 11                 |
|                         |                    | versus streptozotocin + 5-FU               |                          | 0                  |
|                         |                    | nIFN-α × VII/w or s.c.                    | 42                       | 15                 |
|                         |                    | rIFN-2b 5 MU × III/w                      |                          |                    |
| Öberg K, Eriksson B, 1991 [16]    | 111                | nIFN-α 6 MU × III/w s.c.                  | 63                       | 21                 |
|                         |                    | rIFN-2a 3 MU/m² × 3/w                     | 25                       | 17                 |
|                         |                    | versus rIFN-α2 3 MU/m² × 3/w +            |                          | 0                  |
|                         |                    | streptozotocin + adriamycin               |                          | 0                  |
|                         |                    |                                           |                          |                    |
| Total                  | 338                |                                             | 42                       | 11                 |

*Malignant endocrine pancreatic tumors
INTERFERON THERAPY OF NEUROENDOCRINE TUMORS

TABLE 2
Adverse Reactions in 111 Patients Treated with α-IFN

| Adverse Reactions                  | %  | WHO Grade |
|------------------------------------|----|-----------|
| "Flu-like" symptoms                | 89 | 1–2       |
| Weight loss                        | 59 | 1         |
| Fatigue                            | 51 | 1–2       |
| Anemia (< 110 g/l)                 | 31 | 1         |
| Leukopenia (< 2.0 × 10^9/l)        | 7  | 1         |
| Thrombocytopenia (100 × 10^9/l)    | 18 | 1         |
| Elevated liver aminotransferases   | 31 | 1–2       |
| Elevated blood lipids              | 32 | 1–2       |
| Liver steatosis                    | 19 |           |
| Autoimmune reactions               | 20 |           |
| Psoriasis (flare-ups)              | 3  |           |
| Neutralizing IFN-abs               | 6–25|          |

dosages for individual patients might range from 1.5 MU to 10 MU three to seven times per week, subcutaneously. Later on, we could confirm that this method clearly correlated with the therapeutic result as well as induction of 2'-5'-A synthetase (see below). Another important observation is obtained from a study by Hanssen et al. [18], in which they reported increased response rates after tumor reduction by embolization of liver metastases previous to the start of IFN. Therefore, reduction of tumor mass might significantly improve the therapeutic results, which also might indicate that alpha-interferon treatment should be initiated early in the clinical course, when the tumor mass is limited.

ADVERSE REACTIONS

The adverse reactions from alpha interferon are listed in Table 2. They include flu-like symptoms for three to five days, initially, in almost all patients, but these adverse events could easily be prevented by concomitant administration of paracetamol. More severe adverse reactions are fatigue (grade I–II) in about 50 percent of the patients, low-grade weight loss in 59 percent of the patients, and sometimes mental depression. About one-third of the patients might develop increased liver enzymes, which are mainly dose-dependent, and about 20 percent of the patients develop autoimmune reactions [26]. Patients treated with recombinant alpha interferons might develop neutralizing interferon antibodies in various degrees to different IFN preparations, which might abrogate the anti-tumor response (Table 3). In such patients, a change from recombinant interferon to human leukocyte IFN might restore the anti-tumor effect [22].

COMBINATION TRIALS

In a recent study, we combined octreotide and alpha interferon in patients with malignant carcinoid tumors. The design of the study was as follows: The patients started on octreotide 50 μg twice a day, increasing up to 100 μg three times daily. If they did not respond to this dose, alpha interferon was added at a median dose of 3 MU three times per week, subcutaneously. Twenty-four patients were included in the study; 22 patients demonstrated increased urinary 5-hydroxyindole acetic acid (5-HIAA), and 19 patients the classical carcinoid syndrome. By using this combina-
tion, patients who were previously resistant either to octreotide alone, or to alpha interferon alone, demonstrated biochemical responses with complete remission in four out of 22 (18 percent) and partial remission in 13 out of 22 patients (59 percent). In the entire group, 77 percent of the patients experienced biochemical responses with a median duration of 15 months [27]. None of these patients, however, demonstrated any significant tumor reduction. When alpha interferon was withdrawn for any reason, an immediate increase of urinary 5-HIAA as well as clinical symptoms was noticed, and, when alpha interferon was reintroduced, a significant amelioration was noted. These beneficial effects of the combination treatment will be further explored in an ongoing randomized, controlled, multi-center study in patients with malignant carcinoid tumors, where alpha interferon and octreotide are combined from the beginning of therapy.

MECHANISMS OF ACTION OF ALPHA INTERFERON

The anti-tumor effects of alpha interferon include anti-proliferation, apoptosis, differentiation, and cytotoxic/cytostatic effects. Furthermore, alpha interferon clearly demonstrates an immunomodulatory effect by increased expression of class I antigens on tumor cells, development of "autoimmunity," and even carcinoid autoantibodies. Alpha interferon binds to specific cell membrane receptors. Thereafter, the signal is transduced to the cell nucleus via different pathways. An important enzyme in this pathway is interferon-sensitive growth factor 3 (ISGF-3), which exists in a latent form but becomes activated by alpha interferon [28]. After the signal has been transduced to the cell nucleus, it binds to interferon-sensitive response elements (ISREs), where it starts transcription of several interferon-inducible genes. There exist at least 20 interferon-inducible genes, and some of them are involved in the anti-proliferative effects of alpha interferon. Three of these gene products have been studied in our laboratory, namely 2'-5'-A synthetase, P-68 kinase, and Mx-A protein. Both 2'-5'-A synthetase and P-68 kinase induce a degradation of mRNA for various peptides, hormones, and growth factors, which results in inhibition of protein synthesis. We have clearly demonstrated that induction of 2'-5'-A synthetase in vitro in tumor cells is correlated with the clinical biochemical response [29]. Most patients who demonstrated more than a threefold increase of basal 2'-5'-A synthetase levels after administration of alpha interferon clearly respond biochemically, whereas those with lower induction were non-responders. Administration of α-IFN to patients with neuroendocrine tumors results in reduced content of mRNA for chromogranin A in biopsy specimens taken from liver metastases [30]. This reduction is of greater magnitude than a corresponding decrease in the number of tumor cells. The

| Preparation | No. of Patients | "Binding" ab (%) | Neutralizing ab (%) |
|-------------|----------------|------------------|--------------------|
| Hu-Le-α     | 81             | 1 (12)           | 0 (4)              |
| IFN-α2b     | 151            | 18 (12)          | 6 (4)              |
| IFN-α2a     | 26             | 8 (31)           | 7 (27)             |

*aThe antibodies neutralize the antiviral activity of α-IFN in a bioassay.*
fact has been noticed that it takes a long time to normalize the urinary 5-HIAA in many patients (Fig. 1) and that a complete normalization of circulating hormone levels does not necessarily mean a complete eradication of the tumor. Even after eight years of continuous alpha-interferon treatment with normalization of urinary 5-HIAA, there is still visible tumor remaining. This phenomenon is rather unique for

FIG. 1. Treatment of a patient with carcinoid tumor and liver metastases with streptozotocin and 5-FU (S + 5FU) followed by alpha interferon. The vertical bars indicate tumor area in cm², and the curve, urinary 5-HIAA µmol/24 hours.

FIG. 2. Plasma levels of neuropeptide K (NPK) during intra-arterial infusion of 10 MU of recombinant alpha interferon into the feeding artery of metastasis from a patient with carcinoid tumor. The different curves indicate the same procedure, one year apart, showing similar results. The hatched area indicates the reference range for the tachykinin neuropeptide K.
FIG. 3. Administration of a mixed meal in a patient with multiple endocrine neoplasia type 1 and endocrine pancreatic tumors. The different curves indicate serum levels of pancreatic polypeptide during this meal stimulation; the horizontal bar indicates eating of the meal. After 12 months of interferon, the test indicates a complete normalization.

biological response modifiers, and we have demonstrated that, with increasing treatment periods, the number of tumor cells is reduced, whereas the fibrous components of the tumor are increased [31]. These changes will not necessarily result in any change in tumor size seen on computed tomography or ultrasound investigations and must be followed by repeated biopsies. In the near future, the biological activity of a tumor might be studied with positron emission tomography (PET), where accumulation of C11-labeled hydroxytryptophan correlates with the metabolism of the tumor. The anti-proliferative effect of α-IFN has been studied in vivo on biopsies taken from liver metastases. By using the antibody Ki-67, a significant reduction of immunostaining was observed after α-IFN administration, indicating a low proliferation rate [32].

We have previously been able to demonstrate that acute infusion of alpha interferon into the feeding artery of a carcinoid tumor causes a release within 15 minutes of neuropeptide K, one of the peptides produced by carcinoid tumors (Fig. 2). That result might be due to cytotoxic effects, in which the cell death causes a
release of stored peptides. A recent observation is that long-term treatments with alpha interferon, in patients with endocrine pancreatic tumors, might normalize an abnormal meal stimulatory test (Fig. 3) or, in patients with gastrinomas, a secretin stimulatory test (Fig. 4). The reason for such normalization is not quite clear. One possibility might be that malignant cell clones have been destroyed by the interferon treatment, and thus normal endocrine pancreatic cells are left, with normal response to these stimulatory tests.

In summary, alpha interferon has demonstrated a significant anti-tumor effect in neuroendocrine gut and pancreatic tumors. Combination with another biological response modifier, octreotide, seems very promising. Future studies will show the precise role of this combination treatment. Adverse reactions to alpha interferon are mostly dose-dependent, and it is important to individualize the treatment for each patient. Today, predictive testing can be performed using induction of 2'-5'-A synthetase. Positron emission tomography (PET) might be a future tool to follow
these patients on IFN therapy. The treatment with alpha interferon seems to be lifelong, and it is important to realize that the therapy is not curative, but can control the disease for extended periods. Survival seems to be significantly prolonged during alpha-interferon treatment, and it is accompanied by a fairly good quality of life.

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