Should interferon-α and somatostatin analogs be combined in gastroenteropancreatic neuroendocrine tumor therapy?

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Gastroenteropancreatic are the most common of the neuroendocrine tumors. They are usually well differentiated and slow growing, and express subtype 2 and 5 somatostatin receptors in most cases. Both somatostatin anologs and interferon-α were used as single agent, showing symptomatic, biochemical, and in a minority of cases, even antiproliferative activity. *In vitro* and *in vivo* evidence exists supporting the combined use of these drugs, but the only two randomized trials published to date did not show a statistically significant advantage for the combination compared with single-agent use. However, several reports exist from nonrandomized trials that would justify the sequential use of the two drugs or the combination after progression on single-agent therapy. Therefore, larger, international, prospective, randomized and multicentric clinical trials studying homogeneous populations are necessary in order to give a final answer.

Keywords: interferon, neuroendocrine tumors, somatostatin analogs

Neuroendocrine tumors (NETs) represent a very heterogeneous and rare category of neoplasms, accounting for only 0.5% of all malignancies. Gastroenteropancreatic (GEP) NETs are the most common group [1], with gastrointestinal (GI) primary tumors being much more frequent than those that are pancreatic. The ileum has the highest incidence. The typical carcinoid syndrome can be found in less than 20% of carcinoids, particularly mid-gut primary and liver metastases [2]. In rare cases an atypical carcinoid syndrome can be present [3], but in most cases GI NETs are non-functioning. Between 30–40% of pancreatic-NET patients present without hormone-related symptoms; in the other cases, syndromes related to a specific secreted hormone are present [4]. Global prognosis of NET patients is relatively good, with a 5-year survival rate of around 70%, including all sites, stages and types of tumor. Local metastases may allow a considerable 5-year survival rate of 72%, whereas for distant metastases it is only 39%. Among GEP NETs, rectal and appendiceal tumors are associated with the best survival [1].

According to the new World Health Organization (WHO) classification, by Solcia and colleagues, published in 2000, GEP NETs are distinguished in three types:

- Well-differentiated endocrine tumors, that include tumors (or carcinoids) and carcinomas (or malignant carcinoids)
- Poorly differentiated endocrine tumors (or small cell carcinomas)
- Mixed exocrine–endocrine carcinomas [5]

The old classification, including foregut, midgut and hindgut carcinoids [6], should be considered obsolete by now.

Somatostatin analogs

Somatostatin (sst) was discovered by Brazeau and colleagues in 1973 at the Salk Institute in La Jolla, California (CA, USA) [7]. It proved inconvenient for clinical use due to its short half-life and therefore analogs were developed at the beginning of the 1980s [8]. The octapeptide octreotide is the most extensively investigated analog. Other analogs with very similar affinity and activity profiles, such as lanreotide, have been developed [9]. They have a 1 to 2 h half-life and they can be administered subcutaneously, intravenously and intramuscularly. They exert their action interacting with sst receptors. Natural sst binds to all five subtypes (sst-1–5) of receptors, whereas the two analogs bind in particular to subtype 2, and with a somewhat lower affinity to the sst-3 and -5 receptor subtypes. Analogs of sst can inhibit the release of peptides from the tumor but also from the pituitary, intestine and pancreas. Therefore sst-analogs can control hypersecretion in NETs that express sst receptors [9]. In addition, these agents may also exert some antiproliferative activity [10].

Symptomatic and biochemical activities of sst analogs are, by now, well recognized in small-bowel NETs, with a quite high response rate [11,12]. Similar results were reported in gastrinoma [13], Vasoactive Intestinal Peptide-producing tumor (VIPoma) [14], glucagonoma [15], stoma [16]; in insulinoma results were lower because in 50% of cases, sst2 receptors are missing [17].

Table 1. NETs sst analog treatment.

Response release (%)	Standard dose (%) 0.1–1.5 mg/day	High dose (%) >3 mg/day	Slow release 20–30 mg/2–4 weeks
Subjective	64	42	63
Biochemical	63	75	67
Tumor	5	13	3

NET: Neuroendocrine tumor; sst: Somatostatin.

Tumor shrinkage was demonstrated in a very small percentage of cases with standard dose [18–20]. However, in some cases increasing doses translated into major activity [22–24]. Furthermore, dose titration also revealed activity on symptoms and hormone levels (**Table 1**)[25].

The standard dose of octreotide varies from 0.1–3 mg/day, to be administered subcutaneously 2–3 times a day. High dose is more than 3 mg/day. In order to avoid multiple daily subcutaneous injections, a long-acting release (LAR) formulation was introduced, with 10, 20 and 30 mg intramuscular vials to be administered every 4 weeks [26]. These new forms resulted in being as active as the subcutaneous form [27]. Lanreotide is usually administered intramuscularly once every 2–4 weeks, with 30 and 60 mg vials respectively [28]. A slow-release form (Autogel®, Ipsen Ltd) has been studied over the last few years, that could allow an every 6 week administration [29].

Analogs of sst primarily inhibit the secretion of bioactive peptides by the tumor cell in patients with NETs [9]. Whether or not it is mediated via sst-2 and/or sst-5 receptors remains to be established [30]. However, octreotide demonstrated a very high binding affinity to the sst-2 subtype which makes this receptor a likely candidate in mediating the clinical effects of octreotide therapy in GEP NETs. The sst receptor binding activates multiple intracellular mechanisms, such as the adenylate cyclase activity inhibition, with an inhibitory effect on secretion processes [31].

The antiproliferative effect of sst analogs can be due to several mechanisms, including inhibition of growth factor effects on tumor cells, induction of apoptosis [32] and inhibition of angiogenesis at high doses [33].

Interferon

Interferon (IFN)-α was introduced by Oberg and colleagues for the treatment of carcinoid tumors in 1982 [34]. Of the patients with small intestine carcinoid and carcinoid syndrome, six out of nine responded to leukocyte IFN 3 × MIU per day during the first month and 10 MIU per day for another 2 months. Reduction of symptoms and amine levels, without effect on tumor growth, was observed. Later, an antiproliferative effect, in up to 15% of cases, was also reported [35]. Since then, more than 500 patients with NETs have been treated with IFN worldwide. Several studies were published reporting 40–70% of symptomatic, 40–50% biochemical, and 10–15% antiproliferative activities [36–40]. Dose and schedule varied from 3.000.000 IU subcutaneously 3 times a week to 9.000.000 IU subcutaneously daily (**Table 2**).

IFNs represent a large class of agents with antiviral and antitumor activity [41]. They are distinguished into two groups: Type I and II. Type-I IFNs include IFN-α (leukocyte IFN), of which at least 14 different subtypes exist, IFN-β (fibroblast IFN) [42], as well as IFN-ω and IFN-τ. There is only one known Type II IFN (immune IFN) – IFN-γ. Type I IFNs exert their action by binding to a specific receptor, of which two subtypes exist, IFNAR1 and IFNAR2 [43]. IFN-α is the most evaluated of all the IFNs in the treatment of NETs. Its antitumor effect has been studied in many model systems and includes direct antiproliferative as well as immunoregulatory and antiangiogenic effects both *in vivo* and *in vitro* [44]. In NETs the direct antiproliferative effects of IFN-α appear to be mediated via delaying of G1–S phase cell-cycle progression, possibly due to an upregulation of p21 and p27 [45], resulting in the inhibition of the synthesis of bioactive peptides and growth factors. The cell-cycle block is derived from the signal-transduction mechanisms following activation of type-I IFN receptors by IFN-α. They consist of the phosphorylation of Janus kinase (JAK)1, Tyrosine Kinase (TyK)2 and signal transducer and activator of transcription (STAT)1 and 2, and nuclear activation of IFN-stimulated genes (ISGs), including IRF-1, IRF-2, p68 kinase and 2-5-A-synthetase. However, the mechanism(s) of action of the growth-inhibitor effect of Type I IFNs on NET cells are still not completely understood.

Combination trials

IFN-α has been combined with sst analogs, especially octreotide, in order to improve the efficacy of single-agent therapy (**Table 3**). The first

Table 2. NETs IFN-α treatment.

Response	Regular dose 3–9 MU 3–7 times a week
Subjective	40–70%
Biochemical	40–50%
Tumor	10–15%

IFN: Interferon; NET: Neuroendocrine tumor.

evidence of some activity due to the combination of IFN and octreotide rather than the same drugs used as single agent, was reported by Joensuu in 1992 [46]. A 43 year-old man with several symptoms due to a retroperitoneal unknown primary NET, who had been receiving IFN -α-2b, 10 MU subcutaneously three times a week with incomplete symptom control benefited from the addition of octreotide 0.1 mg twice a day. Symptoms totally disappeared and both tended to reappear when octreotide was reduced to 0.05 mg twice a day and IFN was gradually withdrawn. In both cases symptoms disappeared when octreotide dose was increased again and IFN resumed.

In the same year Janson and colleagues reported the efficacy of IFN/octreotide combination in 24 NET patients progressive to octreotide alone [47]. The patient population was quite homogeneous, with 23 of 24 having a midgut carcinoid and 18 of 24 showing a carcinoid syndrome. All patients had a biochemical progression after received octreotide for a median period of 8 months. Of the patients, 10 initially responded to the regular dose but were remaining 14 demonstrated symptomatic or biochemical progression after just 3 months of octreotide. IFN-α addition, with a median subcutaneous dose of 9 MU/week, produced a 77% biochemical response rate, lasting for a median of 12 months (range 5–46). Of the 17 responding patients, 9 had previously been treated with IFN-α but were progressive or intolerant, inferring that the combination is better not only for efficacy but also for tolerability. The authors stated that the benefit is due to the combination and not to IFN alone, because the known biochemical response rate of IFN -α alone is 44% and an increase of biochemical markers occurred when IFN was withdrawn. However, no WHO partial responses, but only four stable diseases, were obtained.

A similar trial was conducted by Frank and coworkers [48] on 21 patients with metastatic GEP NET. In this study the population was less homogeneous than Janson's, including nine intestinal, eight non-functioning pancreatic NETs, and four gastrinomas. All patients had computed tomography (CT)-documented tumor progression before entering the study, and 16 of them had been treated with octreotide 0.2 mg three times a day. The combination treatment with octreotide 0.2 mg three times a day plus IFN-α 5 MU three times a week, yielded an inhibition of tumor growth in 67% (14/21) of patients, lasting for more than 3 months. Thirteen patients had WHO stable disease and one had a hepatic WHO complete response (lasting for 4 years). Median stable disease was 12 months (range: 3–52). Both this study and Janson's demonstrated that the biochemical response does not correlate to the inhibition of tumor growth. Although this was not a Phase III trial, the authors underlined in the discussion that responders had a significantly longer survival (median, 68 months) than nonresponders (median, 23 months). IFN-related side effects were more severe than those attributable to octreotide; however general toxicity was mild and did not require dose reduction. Only 2 patients refused further treatment after 4 months of therapy despite stabilisation of tumor growth, because of IFN-induced flu-like side effects.

In 2002, the Uppsala group reported the results of an IFN/sst analog in 16 patients with metastatic pancreatic endocrine tumors, 8 of which were nonfunctioning [49]. Doses of IFN -α and sst analog were individually titrated with IFN varying from between 9 and 25 MU/week and octreotide and

Table 3. IFN-α/sst analog combination therapy: nonrandomized trials.

Author	N. points	Subjective (%) response n. pts	Biochemical response n. pts (%)	Radiological response n. pts	Refs
Janson *et al.* (1992)	24	NR	17/22 (77)	15	[47]
Frank *et al.* (1999)	21	NR	9/13 (69)	14	[48]
Fjällskog *et al.* (2002)	16	NR	10/16 (63)	11 SD 3 PR	[49]

IFN: Interferon; PR : Partial response; SD: Stable disease; sst: Somatostatin.

Table 4. IFN-/sst analog combination therapy: randomized trials.

Author	No. pts	Arms	Responses			5-y survival	1-y PFS
			Sympt.	*Biochem.*	*Radiol.*		
Kölby (2003)	68 (1991–1998)	IFN OCT + IFN	NR	NR	NR	36.6%, 56.8%, HR 0.62 (CI; 95% 0.3–1.1, p = 0.132)	
Faiss (2003)	80 (1995–1998)	IFN LAN IFN + LAN	Better p = 0.037	No Diff	PR 4 SD 28 PR 4 SD 26 PR 7 SD 18		No. Diff

Biochem.: Biochemical; CI: Confidence interval; HR: Hazard ratio; IFN: Interferonl; LAN: Lanreotide; NR: Not reported; OCT: Octr.eotide; PFS: Progression-free survival; PR: Partial response; Radiol.: Radiological; SD: Stable disease; Sympt.: Symptomatic.

lanreotide between 0.1–1.5 and 6 mg daily respectively. Of the 16 patients, 8 had previously received IFN alone, 6 had received analogs alone, and 7 IFN or analog plus chemotherapy. All patients were defined as progressing when starting the new treatment, but the kind of progression, radiologic or biochemical, is not specified. A partial response (PR), according to the WHO criteria, was seen in three patients (19%), with a median duration of 23 months (range 19–25), and a stable disease (SD) in 11 patients (69%), with a median duration of 13 months (range 4–32). Among the eight patients previously progressing on IFN alone, one PR and five SD were obtained; whereas all patients previously progressing on sst analog demonstrated a SD. The biochemical response rate was 38% among IFN-progressing patients and 33% among sst analog patients. All three patients previously progressing on both IFN and sst analog as a single drug achieved a biochemical and radiologic stabilization of the disease with the combination. All side effects were mild except for two patients experiencing Grade III cortical neurologic toxicity. The authors conclude that the combination of IFN and sst analog can be proposed to patients progressing on single treatment with IFN or sst analog, or to patients who fail during chemotherapy. However, the radiologic response evaluation is suboptimal in this study, considering that two patients were only examined with ultrasonography and in 2 other patients, CT examinations were misplaced. Furthermore, toxicity should be considered as a possible factor limiting the feasibility, at least at some doses of IFN, given that 3 of 16 patients ended the treatment because of Grade II–III side effects.

All three studies above led to propose a better activity for the combination than for single-agent therapy. However, it is not possible to conclude as to a real impact on survival. Therefore, a randomized trial was conducted by Kolby and colleagues to study the effect of IFN addition to octreotide on survival [50]. A total of 68 patients with metastatic mid-gut carcinoid were included in ten centers between 1991 and 1998 (**Table 4**). All patients had previously had their primary tumors operated on and treated with transarterial chemoembolization (TACE) before having been randomized to either octreotide or a combination of octreotide and IFN-α. An overall 5-year survival rate of 46.5% during a follow-up period of 33–120 months was obtained. No statistically significant difference in survival between the two groups resulted, even though in the IFN + octreotide group, 5-year survival was longer than in the octreotide group (56.8 and 36.6%, respectively). As for the risk of tumor progression, that was the other objective of this study. Patients treated with octreotide and IFN-α had a significantly lower risk of progressive disease (HR 0.28, 95% CI 0.16–0.45; p = 0.008). Of the 25 patients reported to have tumor progression, 19 were treated with octreotide alone compared with 6 who received the combination.

The only other prospective randomized trial on the IFN-α/sst analog combination was published in July 2003 in the *J. Clin. Oncol.* by Faiss and colleagues [51]. Between 1995 and 1998, 84 patients with CT- or ultrasound (US)-documented progressive metastatic NETs were randomized to one of the following three groups:

- Lanreotide 1 mg subcutaneously three times a day
- IFN-α 5 MU subcutaneously three times a week
- A combination of the two drugs at the same doses

The main objective of this study was the 1-year progression-free survival (PFS) rate. Sample-size calculations were based on the hypothesis that a 1-year PFS rate of patients with metastatic

NETs treated with IFN is lower (15%) than the corresponding rate of patients with lanreotide (25%) and that the combination of the two drugs (45%) is superior to the corresponding monotherapies. The population of patients was quite heterogeneous, and most diseases were nonfunctioning. Although there were more PRs in the combination arm compared with the single-agent arms (2, 1 and 1, respectively), no significant difference in rates of PR, SD and progressive disease (PD) between the three arms was recorded. However, one of the 11 patients progressing on lanreotide and shifted to the combination showed a clear reduction in the rate of tumor growth. Furthermore, a statistically significant reduction of symptoms was only observed in the combination arm ($p = 0.037$, Wilcoxon test). Biochemical response did not differ among the treatment groups, and this study showed once again that it was not correlated with inhibition of tumor growth. Combination therapy seemed to be more toxic than monotherapy with 7 out of 28 patients who had to stop treatment compared with 4 out of 27 in the IFN arm and 3 out of 25 in the lanreotide arm. However, difference in time of study between the three arms was not statistically significant ($p = 0.337$, Kruskal–Wallis test).

Some criticisms were addressed in this study and have not been completely clarified by the authors' reply. Fazio and Oberg remarked that in this study, it is not clear if all patients were evaluated by CT-scan, as requested by the WHO [52]. In addition, this is a drawback also found in Fjällskog, Kölby, and Janson's trials. Unfortunately, US is a very operator-dependent examination and therefore it should not be used alone for response evaluation. Considering the very low PR rate in NETs, even very small differences can be crucial to conclude for the activity of some drugs, and therefore a less subjective examination should be used to evaluate the response, all patients undergoing the same kind of examination. Other criticisms were raised by Volter and Peschel regarded the statistical aspects of this study [53]. In particular, it was closed after 80 patients instead of the 105 originally planned. Furthermore, it is not clear on what the authors based their reasoning for the use of 15% of PFS at 1 year for IFN and 25% for lanreotide. Finally, heterogeneity of patients and lack of optimization of treatment were other points of criticisms.

Conclusion

Clinical trials to study the efficacy of IFN and sst analogs in combination are supported by some *in vitro* and *in vivo* evidence. *In vitro* studies described an upregulation of sst receptors by IFN [54]. Furthermore, IFN downregulates the mRNA expression of peptides and hence reduces hormone production, whereas sst analogs act more by reducing the release of peptides. The two cyclin-dependent kinase inhibitors p21 and p27, involved in the cell-cycle block in the G2–S phase induced by IFN, can be upregulated by sst analogs [55,56,57]. A reduction in growth factors and their receptors and antiangiogenic activity can be effected by both drugs. Finally, IFN and sst analog in combination has been shown to have a stronger antiproliferative effect than either drug alone, in an *in vivo* model with xenografted BON cells [32].

Nevertheless, so far it has not been definitively clarified if the combined use of IFN-α and sst analog is more effective than the use of the same drugs as a single agent. Some nonrandomized studies indicate that there is and additive effect of the combination, but on the other hand the only two randomized trials published so far did not conclude in the same way.

Therefore, we do not have at present enough statistical evidence for an upfront use of the combination of IFN-α and sst analog, but we have some clinical evidence coming from the few studies conducted so far that would justify the sequential use of the two drugs or the combination after progression on single-agent therapy. To have a conclusive response, larger clinical trials in international, prospective, randomized, multicenter settings studying homogeneous populations are necessary. However, it would require the participation of every major center with specific expertise in NETs.

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