JPP Journal of Pharmacy and Pharmacology

JPP 2006, 58: 1623–1628

Received June 1, 2006
Accepted August 14, 2006
DOI 10.1211/jpp.58.12.0009
ISSN 0022-3573

Cyto-reduction of neuroendocrine tumours using Sandostatin LAR® in combination with Infergen®: results of a case series

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Abstract

Historically, limited trials evaluating biotherapy in treating metastatic neuroendocrine tumours have yielded mixed results. In this study, the efficacy of a novel combination therapy featuring long-acting Sandostatin LAR® plus α-interferon was evaluated. In a prospective case series, 12 patients with unresectable metastatic neuroendocrine tumours refractory to treatment initiated therapy with Infergen® and Sandostatin LAR®. Radiological response was followed serially at 3-month intervals. A biochemical response was considered significant if marker levels decreased by ≥50% compared with baseline. Inhibition of tumour growth lasting for greater than 3 months (mean response 22.6 ± 17.7 months) was seen in eight patients. Complete tumour regression was observed in one patient, lasting for 40 months; three patients exhibited partial tumour regression (mean response 29.3 ± 24.0 months), and four patients maintained a stable tumour response (mean response 13.3 ± 9.2 months). Four patients showed no response to therapy (mean response 5.0 ± 6.0 months). All enrolled patients are alive currently. The biochemical response seen in seven patients did not correlate with the radiological response. These results suggest that the novel combination of long-acting Sandostatin LAR® with an α-interferon may be at least as effective as either combination therapy with short-acting octreotide or monotherapy with Sandostatin LAR®.

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Acknowledgment: We thank Dr George Sachs for his critical review of the manuscript. Financial disclosures: none.

Introduction

The most important step in the management of neuroendocrine tumours (NETs) is to first determine the extent of disease (Pisegna et al 1993a). The presence of liver metastases is perhaps the most important determinant in the prognosis of patients with this disease (Jensen 1999). If hepatic metastases are present on imaging studies, the growth rate must be assessed, as a subset of patients may have stable disease over a long period of time. For those NETs with documented progression, therapy should be aimed at reducing tumour bulk (Caplin et al 1998; Chung et al 2001). Historically, strategies to decrease tumour burden have included surgery, radiofrequency ablation, chemoembolization (Clouse et al 1994), chemotherapy (Moertel et al 1992) and, more recently, radiopharmaceutical therapy with ^{111}Indium octreotide or 90Y-DOTA-lanreotide (Oberg 1998), though no single best effective therapy has been established to date.

Recently, new medical antiproliferative strategies have centered on biotherapy. As monotherapies, daily dosed octreotide and α-interferon (α-IFN) have generally had limited success in tumour inhibition (Kaltsas et al 2004), though recent trials involving long-acting octreotide have shown high rates of tumour stabilization comparable with that achieved with combination therapy (Ricci et al 2000; Tomassetti et al 2000; Welin et al 2004). To date, five prospective European trials featuring combination therapy have been published, with mixed results (Frank et al 1999; Fjallskog et al 2002; Kolby et al 2003; Faiss et al 2003; Arnold et al 2005). Two prospective studies have clearly demonstrated the efficacy of combination therapy: Frank et al (1999) reported a 67% tumour inhibition rate, while Kolby et al (2003) reported an 82% tumour stabilization rate in patients on combination therapy with octreotide and α-IFN.

In contrast, three other European studies have reported less efficacious results with combination therapy. Fjallskog et al (2002) reported only a 19% radiological response rate to

combination therapy for a median duration of 23 months. Faiss et al (2003) concluded from a large, prospective, randomized, multicentre study that combination therapy had comparable antiproliferative effects (25% tumour inhibition) with either monotherapy with lantreotide (32% tumour inhibition) or α-IFN (30% tumour inhibition) alone. The low tumour inhibition response rates in both studies may have resulted from suboptimal treatment dosages in the former and lack of patient homogeneity in the latter. More recently, Arnold et al (2005) randomized patients to either monotherapy or combination therapy with short-acting octreotide and concluded that combination therapy was not superior in terms of progression-free and long-term survival, despite marked differences in disease progression at 12 months after randomization.

Given these conflicting results, we sought to further characterize the efficacy of combination therapy in NETs. In an effort to add to the growing literature on biotherapy, we evaluated a novel combination therapy featuring long-acting octreotide (Sandostatin LAR®; Novartis, Switzerland) plus α-IFN (Infergen®; Amgen Inc., Thousand Oaks, CA USA) in 12 patients with NETs in the first study involving patients from a US population. Based on data from studies evaluating long-acting octreotide monotherapy in NETs (Rubin et al 1999; Wymenga et al 1999; Ducreux et al 2000; Aparicio et al 2001), we hypothesized that combination therapy with Sandostatin LAR® and α-IFN would be as effective, if not more so, as combination therapy with short-acting octreotide and α-IFN.

Materials and Methods

Patient selection

The clinical characteristics of the enrolled patients are listed in Table 1. All patients with NETs metastatic to the liver that were considered surgically unresectable were eligible for the study. Patients previously treated with octreotide were also eligible. All enrolled patients met inclusion criteria, including histologically proven metastatic NETs and documented progression of tumour size during the 3 months prior to enrolment based on imaging studies.

Nearly all of the patients exhibited a moderate rate of tumour progression, defined as an increase in tumour size between 25–50%, and one patient (Patient 10) experienced rapid tumour progression (increase in tumour size >50%) during the 3 months prior to enrolment. Mean time from diagnosis to enrolment was 19.3 ± 10.4 months for all patients (responders 20.5 ± 8.0 months; non-responders 16.8 ± 10.3 months). Eight of 12 patients had a prior surgical history. The majority of patients had carcinoid NETs (7) with primary tumours found in the pancreas (8).

Study design and statistical analysis

The study was conducted between October 2000 and December 2004 as a prospective, non-randomized, single-centre, open-label Phase I/II dose escalation study of Sandostatin LAR® in combination with a fixed dose of Infergen®. This study was approved by the Office for Protection of Research Subjects at the David Geffen School of Medicine at UCLA. Patients were followed serially at 3-month intervals with imaging (magnetic resonance imaging, computed tomography, or both) and laboratory exams. Response to therapy was determined based on biochemical and radiological criteria.

Patients initiated therapy with a fixed dose of Infergen® (9 μg 3 times weekly subcutaneously) and Sandostatin® (200 μg 3 times daily subcutaneously) for a period of 28 days. Two weeks after initiation, injections of Sandostatin LAR® were initiated at a dose of 20 mg once a month (Level 1). This was increased to 30 mg once a month (Level 2) if there was no response or if disease progression was observed at the 3-month evaluation. If a patient failed to demonstrate tumour response by Month 6, the patient was discontinued from the study. Patients who demonstrated a response continued on the same dose.

Quantitative results were recorded as means $\pm$ s.d. Statistical analysis was performed using a paired *t*-test to assess differences between subgroups analysed. Differences were

Table 1 Clinical characteristics of the patients studied

Patient no.	Sex	Age (years)	Tumour subtype	Months since diagnosis	Primary location	Surgical history	Metastases at surgery
1	Male	44	Carcinoid	15	Unknown		Yes
2	Male	59	Carcinoid	22	Jejunum	Removal of primary	Yes
3	Male	33	Non-functioning	12	Pancreas		Yes
4	Female	54	Carcinoid	16	Jejunum	Removal of primary	Yes
5	Male	46	Glucagonoma	24	Pancreas	Whipple procedure	No
6	Female	42	Gastrinoma	27	Pancreas	Whipple procedure	Yes
7	Male	40	Insulinoma	16	Pancreas	Search for primary	Yes
8	Male	59	Non-functioning	35	Pancreas	Search for primary	Yes
9	Female	52	Carcinoid	12	Thymus	Removal of primary	Yes
10	Female	49	Carcinoid	6	Pancreas		Yes
11	Male	69	Carcinoid	19	Pancreas		Yes
12	Female	52	Carcinoid	30	Pancreas	Whipple procedure	Yes
		49.9 ± 9.8 (mean $\pm$ s.d.)		19.3 ± 10.4 (mean $\pm$ s.d.)			

considered to be significant when the calculated P value was 0.05 or less.

Radiological response

Complete tumour regression was defined as the absence of a detectable tumour mass using any radiographic imaging modality. Partial tumour regression was defined as a reduction by ≥25% in diameter of the largest measurable tumour mass, with no increase in size of any other mass. Tumour stability was defined as <25% increase in any measurable malignant lesion, with no new lesions on any imaging modalities. Tumour progression was defined as a >25% increase in diameter in any malignant lesion or the development of new lesions.

Biochemical response

Tumour responses were assessed biochemically by comparing marker levels at 3 months after treatment with pre-treatment values. A ≥50% decrease in serum chromogranin A ($ng\,ml^{-1}$) or gastrin ($pg\,mL^{-1}$) levels in patients was defined as a positive biochemical response. Both chromogranin A and gastrin can be measured with sensitive assays and changes in serum levels with time can be correlated to tumour extent (Goebel et al 1999).

Results

Radiological response

Inhibition of tumour growth lasting for greater than 3 months was noted in eight of the 12 (67%) patients (mean response 22.6 ± 17.7 months; range 3 to 53 months); four patients showed no long-term response to combination therapy (mean response 5.0 ± 6.0 months; range 0 to 12 months) (Table 2). Complete tumour regression was observed in one individual (Patient 3), with complete disappearance of a prior pancreatic mass lasting for over 3 years (Figure 1). Three patients (Patients 2, 6 and 7) experienced partial tumour regression (mean response 29.3 ± 24.0 months), while four patients (Patients 1, 4, 5 and 8) maintained a stable tumour response (mean response 13.3 ± 9.2 months).

All enrolled subjects are alive currently, and two patients (Patients 6 and 8) continue on combination therapy. Another responder (Patient 3) who experienced complete tumour regression ended the study to begin combination therapy with Sandostatin LAR® and pegylated α-IFN. Four other responders (Patients 1, 4, 5 and 7) discontinued the study either to seek new treatment elsewhere or due to the cost of combination therapy. One responder (Patient 2) withdrew due to intolerable side-effects from the α-IFN therapy. Of the non-responders, one sustained a partial response (Patient 9) and one stable growth (Patient 11) prior to disease progression. Of the two patients who failed to demonstrate any response to combination therapy (Patients 10 and 12), one (Patient 10) was noted to have rapid progression of disease prior to enrolment.

Patients with non-carcinoid tumours (mean response 30.0 ± 18.7 months) experienced a significantly greater mean radiological response to combination therapy compared with patients with carcinoid tumours (mean response 7.3 ± 6.2 months) ($P < 0.05$). In addition, all four non-responders in this study had carcinoid tumours. In contrast, patients with a prior surgical history (mean response 18.0 ± 17.6 months) experienced a similar mean radiological response to combination therapy as those without a prior surgical history (mean response 14.3 ± 17.6 months) ($P > 0.05$).

Biochemical response

A biochemical response (≥50% decrease in the dominant hormone level) was observed in seven of the 12 patients (58%) when enrolment chromogranin A ($ng\,mL^{-1}$) or gastrin ($pg\,mL^{-1}$) values were compared with values after 3 months

Table 2 Comparison of the duration of tumour inhibition (in months) in 12 patients on combination therapy with Sandostatin LAR® and α-interferon

Patient no.	Number of months with tumour inhibition	Number of months on combination therapy	Radiological response
1	9	9	Stable
2	5	5	Partial responder
3	40	40	Complete responder
4	17	17	Stable
5	3	3	Stable
6[a]	53	53	Partial responder
7	30	30	Partial responder
8[a]	24	24	Stable
	22.6 ± 17.7 (mean ± s.d.)	22.6 ± 17.7 (mean ± s.d.)	
9	12	16	Non-responder
10	0	3	Non-responder
11	8	13	Non-responder
12	0	12	Non-responder
	5.0 ± 6.0 (mean ± s.d.)	11.0 ± 5.6 (mean ± s.d.)	

Patients were labelled as complete responders, partial responders, stable responders or non-responders based on serial radiological evaluation. All 12 patients are alive currently. [a]Patients who continue on combination therapy currently.

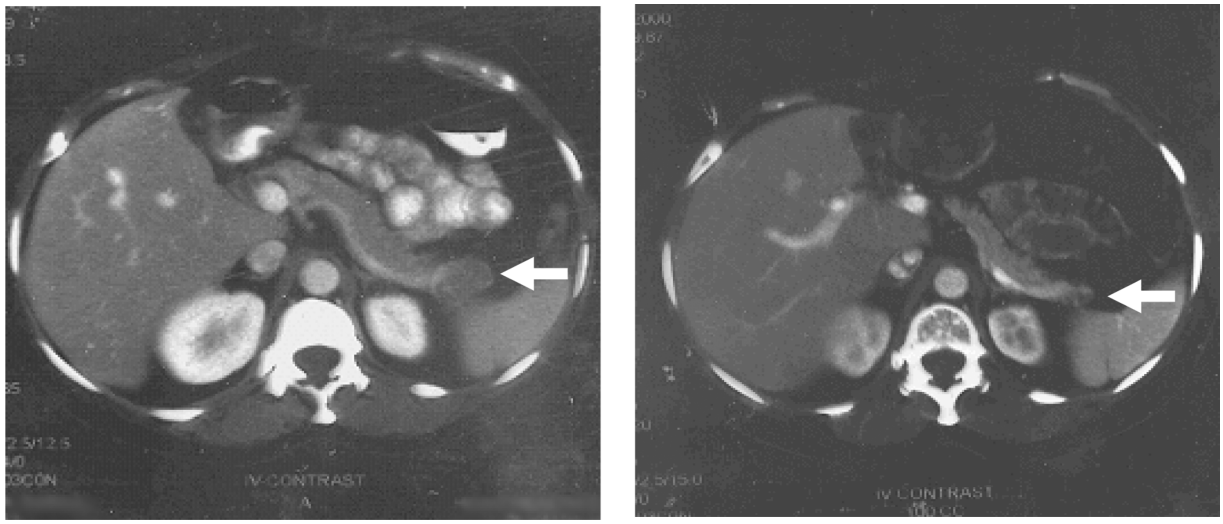

Figure 1 Complete tumour regression of a pancreatic neuroendocrine tumour observed in one individual (Patient 3). Baseline abdominal computed tomography (left) depicting a mass in the pancreatic tail with total resolution (right) following 10 months of combination therapy with Sandostatin LAR® and α-interferon. Patient 3 now continues on combination therapy with Sandostatin LAR® and pegylated α-interferon.

of combination therapy (Table 3). This biochemical response, however, did not correlate with inhibition of tumour growth as assessed radiologically, as four of the five biochemical non-responders exhibited either partial regression or stable tumour growth when visualized by serial computed tomography examination.

Tolerability

In general, combination therapy was very well tolerated. The most common complaints included diarrhoea (seven patients), fever (six patients), headaches and arthralgias (five patients). Only one patient (Patient 2) withdrew from the study after 5 months of the combination therapy due to intolerable side-effects of α-IFN therapy that interfered with his ability to work.

Discussion

This is the first reported US case series prospectively evaluating the efficacy of a novel combination of long-acting octreotide (Sandostatin LAR®) and α-IFN in patients with NETs. The study enrolled 12 patients with progressing carcinoid or islet cell tumours as documented over a preceding 3-month period. Although biologically heterogeneous, NETs of the duodenum and pancreas share comparable response rates with either octreotide or α-IFN monotherapies, and have been shown to progress in a parallel fashion as more than two-thirds of patients with NETs of the duodenum and pancreas will eventually develop liver metastases (Proye & Lokey 2004).

Table 3 Serum chromogranin A (ng mL^{-1}) measured at enrolment and at Month 3 of combination therapy

Patient no.	Biochemical marker on enrolment	Biochemical marker at Month 3	Percent change	Biochemical response
1	6050	6100	+1%	No
2	23.7	12	−50%	Yes
3	25.1	10.3	−59%	Yes
4	2040	2100	+3%	No
5	27.3	16.4	−40%	No
6[a]	2650	147	−94%	Yes
7	40	17.8	−56%	Yes
8	17	35.2	+107%	No
9	96	41.3	−57%	Yes
10	67	15.8	−76%	Yes
11	296	493.2	+67%	No
12	122	46	−62%	Yes
	954.5 ± 1833.4 (mean ± s.d.)	752.9 ± 1786.0 (mean ± s.d.)	−0.26% ± 0.60% (mean ± s.d.)	

Biochemical response was positive if a ≥50% decrease in biochemical marker was observed. [a]Indicates gastrinoma; serum gastrin (pg mL^{-1}) measured instead.

Although no single antiproliferative agent or strategy has been established as superior to date, biotherapy has been advocated by many for the treatment of inoperable, well-differentiated, metastatic NETs (Oberg et al 1983; Pisegna et al 1993b). As a monotherapeutic agent, daily dosed octreotide can reliably control hormone-mediated symptoms of NETs. However, as an antiproliferative agent, its success has been modest, with reported tumoural response rates generally varying between 5% and 11% (Kaltsas et al 2004). Recent studies using long-acting formulations have suggested greater rates of tumour stabilization (40–87.5%) but not tumour regression (0–7%) over a limited study period (10.7–12 months), suggesting that monotherapy may be as effective as combination therapy, however additional trials are needed (Ricci et al 2000; Tomassetti et al 2000; Welin et al 2004).

Somatostatin's inhibitory effects on NETs are thought to be mediated through binding to receptor subtypes *sst*2, *sst3* and *sst*5 but not to *sst*4 (Lamberts et al 1996). In particular, receptor subtype *sst2* is important both because it is the predominant subtype expressed in neuroendocrine tumours (Reubi et al 1996) and because in-vitro studies have shown that *sst2* mediates the antitumour effect of somatostatin analogues (Delesque et al 1997). High-affinity somatostatin receptors have also been identified in peritumoural veins in various carcinomas (Denzler & Reubi 1999), suggesting a role in inhibiting tumour angiogenesis. Furthermore, somatostatin inhibits endocrine-mediated neuroendocrine cell proliferation.

As a monotherapeutic agent, the median tumoural response rate with α-IFN has been reported to be approximately 11%, determined by analysing 13 studies involving 383 patients (Oberg 2000). α-IFN is thought to exert its antiproliferative effects through activation of Janus tyrosine kinases 1 and 2, which activates the Stat transcription factor family to inhibit DNA synthesis and colony formation (Grander et al 1997). Other effects of α-IFN include up-regulation of both p21 and p27, negative regulators of the cell cycle (Hobeika et al 1997; Zhou et al 1999), and induction of fibrosis within liver metastases (Oberg 2000). Polyethylene glycosylated recombinant interferons appear promising because they cause fewer adverse reactions while having the added benefit of an easier weekly administration schedule.

In a limited analysis, patients with carcinoid tumours had a longer duration of response to combination therapy compared with those with non-carcinoid NETs ($P < 0.05$). This differs from previous findings by Frank et al (1999) who reported a greater duration of response in the carcinoid subset. Although it is unknown whether or not one entity responds better than any other, any differences between these studies could easily result from the limited sample size of each study. Also, a subset of carcinoid tumours are known to act in a malignant fashion, metastasizing to the liver and could be the cause of the poor response observed in this study. Given the limited number of functional and non-functional pancreatic NETs in this study, no specific islet cell subtype could be identified as having a greater mean response to combination therapy. Similarly, no differences in mean response rates were seen between patients with and without a previous surgical history.

For the first time in a US population, we characterize 12 patients with progressive NETs on combination therapy with long-acting octreotide (Sandostatin LAR®) and α-IFN. Although no analysis of survival benefit could be done, it is interesting to note that all 12 enrolled patients have survived for at least 4–6 years since their initial diagnosis. We postulate that this greater survival rate may result from an earlier initiation of combination therapy, since all 12 were enrolled in this study relatively early in their diagnosis (mean enrolment 19.3 ± 10.4 months after histological diagnosis). This is corroborated by data showing that preceding octreotide monotherapy is a favourable prognostic factor in tumour response and by data from a Norwegian study suggesting that reduction of tumour mass, either with prior embolization or earlier initiation of treatment, may significantly improve therapeutic results (Jacobsen et al 1995). A prospective randomized trial assessing the efficacy of combination therapy with long-acting octreotide and pegylated α-IFN may reveal an even more efficacious response with fewer additional side-effects and would therefore be a reasonable treatment choice for patients presenting with metastatic NETs.

Conclusions

We treated 12 patients with NETs with long-acting octreotide (Sandostatin LAR®) and α-IFN and report a 67% response rate (tumour stabilization, partial tumour regression, complete tumour regression) for a mean of 22.6 months, confirming that combination therapy is an effective treatment for patients with inoperable, well-differentiated, metastatic NETs. In addition, we have combined for the first time long-acting octreotide (Sandostatin LAR®) with α-IFN to show that this novel combination therapy appears to be at least as effective as either combination therapy with short-acting octreotide or monotherapy with long-acting octreotide, given greater survival rates as observed in this study. In a limited analysis, we have shown that non-carcinoid patients had a significantly greater mean response rate (30.0 ± 18.7 months) compared with carcinoid patients (7.3 ± 6.2 months) to combination therapy ($P < 0.05$). Consistent with previously published data, the biochemical response in these 12 patients did not correlate with the radiographical response as only four of seven patients with a biochemical response also showed a radiographical response.

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