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DOTTORATO DI RICERCA IN
TERAPIE AVANZATE BIOMEDICHE E CHIRURGICHE
XXXI CICLO

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Tesi di Dottorato

A PHASE II, SINGLE-CENTER, PROSPECTIVE, OPEN-LABEL STUDY WITH HIGH-DOSE SOMATOSTATIN ANALOGS (SSA) IN PATIENTS WITH PROGRESSIVE NEUROENDOCRINE TUMORS (NET)

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Introduction

Epidemiology and classifications of neuroendocrine neoplasms

Neuroendocrine neoplasms (NEN) are a heterogeneous group of malignancies, arising from the diffuse neuroendocrine system, with variable histology and clinical behavior. In the last decades the incidence of NEN has considerably increased from 1.09 per 100,000 in 1973 to 6.98 per 100,000 and this increase occurred across all sites, stages, and grades (1). Since the diffuse neuroendocrine system is located in almost every tissue, NEN can virtually occur in any organ of the human body, but the predominant site of localization is the gastrointestinal tract (67%), followed by the bronchopulmonary tract (25%). NEN are mostly sporadic (~80%) but may be associated to genetic syndromes as multiple endocrine neoplasia type 1 (MEN1), von Hippel Lindau syndrome (VHL), neurofibromatosis type 1 and tuberous sclerosis. Age of onset is considerably variable, but NEN more frequently occur in the sixth decade, except when related to inherited syndromes, when their onset is significantly anticipated (2). Although NEN have mainly an indolent course, about 50% of newly diagnosed patients already present with metastases, requiring an effective systemic treatment to prolong survival. Liver, lymph nodes and bone represent the most common sites of metastases. The identification of metastases has a negative impact on prognosis, as in patients with localized disease, 5-year survival rates range from 78% to 93%, while in metastatic NEN, 5-year survival is poor, between 19% and 38%, although survival has increased over the last two decades (3, 4).

As stated by the last World Health Organization (WHO) classification, gastroenteropancreatic (GEP) NEN are divided into three categories with increasing malignant potential, according to proliferative activity as defined by Ki67 index: well differentiated G1 neuroendocrine tumors (NET) (Ki67 ≤2%), moderately differentiated G2 NET (Ki67 3-20%), and poorly differentiated G3 or neuroendocrine carcinoma (NEC) (Ki67>20%) (5) (Table 1). The grading system mainly determines the therapeutic strategy and prognosis of NEN, since histologic differentiation and proliferative activity are the strongest predictors of survival. According to the 2015 WHO classification, thoracic neuroendocrine tumors are classified into typical carcinoid, atypical carcinoid, large-cell neuroendocrine carcinoma,

and small-cell neuroendocrine carcinoma, based on the mitotic activity and the presence/absence of necrosis (6) (Table 2). The knowledge of genetic alterations is now expanding, thus allowing new insight into the molecular basis of NEN and hopefully new classifications will take these aspects into account.

Clinical presentation

Clinical presentation of NEN is widely variable mainly according to site of origin, stage of disease and hormone secretion. NET are usually slow-growing and frequently (~70%) non-functioning, with nonspecific clinical presentation as local symptoms caused by mass effect or obstruction and bleeding. Diagnosis of non-functioning NET can be often delayed or even incidental, when metastases have already developed.

About 25-30% of NET are functional, mainly arising in the digestive system, and manifest with specific syndromes related to hormone secretion. The diagnosis of functional NET requires the demonstration of an inappropriate elevation of specific serum markers together with distinct clinical symptoms (7). Functional NET are typically well differentiated G1 and G2 tumors arising in the endocrine pancreas or the small intestine. The most common NET-related clinical syndromes are carcinoid syndrome, hyperinsulinemic hypoglycemia, and the Zollinger-Ellison syndrome. Carcinoid syndrome occurs in approximately 30-40% of patients affected by midgut NET, though its real incidence is difficult to assess and widely varies in different studies. Carcinoid syndrome mainly presents with recurrent skin flushing, diarrhea, and fibrotic valvular right heart disease, mediated by serotonin secretion, thus 24-h urinary excretion of the downstream serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) is elevated in affected patients (8). Hypoglycemic hyperinsulinemic syndrome is characterized by inappropriate increased levels of insulin in the presence of low plasma glucose concentrations and commonly occurs in pancreatic insulinomas. The Zollinger-Ellison syndrome is characterized by recurrent peptic ulcers, diarrhea and malabsorption due to hypergastrinemia induced by a gastrin-secreting duodenal-pancreatic NET. Clinical syndromes due to vasoactive intestinal peptide (VIP), glucagon or somatostatin-secretion are rare. Other rare entities include the paraneoplastic secretion of ACTH/CRH (adrenocorticotropic hormone/corticotropin-releasing hormone), GHRH (human growth hormone-releasing hormone), PTHrp (parathyroid hormone-related protein), calcitonin (9) (Table 3). Symptoms of functional NET may allow early detection, but on the other hand the effects of hypersecretion can increase

mortality (10). Since the clinical presentation, natural history and prognosis widely differ among NET, there is a critical need to identify accurate diagnostic, prognostic and predictive biomarkers. About 40 circulating analytes of varying sensitivities and specificities have been developed in the last decades, but hormonal workup should always be guided by the presence of symptoms arising from excess hormone production (11, 12). Chromogranin A (CgA) is the most widespread NET biomarker, a constitutive product of the neuroendocrine secretory granule, which can be measured in serum or plasma. The sensitivity of CgA is about 60-90%, but its specificity is less than 50%, due to possible raise in many other common conditions as renal failure, cardiac disease, non-neuroendocrine tumors, and therapy with proton-pump inhibitors. The urinary metabolite of serotonin, 5-HIAA is a reliable marker of carcinoid syndrome of predominantly midgut origin. Other biomarkers of specific tumor syndromes are insulin for insulinoma and gastrin for gastrinoma respectively (Table 4).

NEN management hopefully requires a multidisciplinary approach involving assessment by a surgeon for resection, and systemic or locoregional treatment in cases of unresectable or recurrent disease. Treatment decision in NEN should consider tumor differentiation, grade and stage as well as concomitant symptoms, mainly mass effect and hormone production, along with patients' characteristics, as age, performance status and life expectancy. In the choice of the therapy, care must be taken to the quality of life of patients, balancing potential risks and benefits. Due to the long natural history, patients are often treated with more therapeutic lines. Besides surgery, first-line therapy is usually represented by somatostatin analogs (SSA), and after progression targeted therapies (everolimus and sunitinib), chemotherapy, peptide receptor radionuclide therapy (PRRT) are used in different sequences of treatment (13).

Therapy with somatostatin analogs

Native somatostatin consists of two cyclic peptides of 14 and 28 amino acids with inhibitory role in several functions, including gastrointestinal motility and the secretion of pancreatic and intestinal hormones. The extremely short half-life of native somatostatin (<3 min) and the post-infusion rebound hypersecretion of hormones limit its clinical usefulness (14). The demonstration of somatostatin receptors on the surface of most NET's cells has led to the development of synthetic SSA, whose introduction in clinical practice represented a turning point in NET therapy (15). The two commercially available SSA, namely octreotide and lanreotide, are usually the first-line therapy in patients with well or moderately differentiated NET, due to their inhibitory activity in controlling hormone excess and related syndromes. Both octreotide and lanreotide show high affinity for

somatostatin receptor subtypes (SSTR) 2 and 5, and are now available for either short or long acting release (LAR) formulations. The availability of LAR formulations administered once monthly instead of requiring daily subcutaneous (s.c.) injections, represented a major clinical breakthrough. The introduction of SSA in clinical practice resulted in a substantial improvement of patients' quality of life and survival. Indeed, the comparison of survival rates in patients who received diagnoses of NET from 1973 to 1987, with those who received diagnoses from 1988 to 2004 showed improvement among patients with metastatic disease (HR 0.67; 95% CI, 0.62 to 0.73; P.001). Since octreotide was the only new drug introduced for NET treatment during this period (in 1987), it was the introduction of SSA to have a positive impact on the survival of NET patients (3).

Octreotide and lanreotide are effective in controlling most NET endocrine syndromes. In functioning NET, it is reported a complete or partial clinical response in 70-90% of patients and usually at least 50% of patients with clinical symptoms respond to SSA (14, 16, 17). Furthermore in vitro studies have documented an antiproliferative effect of SSA through both direct and indirect mechanisms (18-20). Initially the antiproliferative effect has been highlighted for short acting SSA in some small series and case reports (21-24) showing significant reduction or complete regression of tumor and metastases. Nevertheless, in most studies, stabilization is reported as best tumor response in about 50% of patients treated with SSA in mono or combined therapy (16, 25, 26).

The role of SSA in the therapeutic management of NET has expanded in the last years. Two phase III clinical trials, namely PROMID and CLARINET, have clearly documented an antiproliferative effect for octreotide and lanreotide respectively (27, 28). In particular, the PROMID study demonstrated that administration of octreotide LAR 30 mg monthly allowed to obtain a 2-fold prolongation of the time to tumor progression in patients with well-differentiated metastatic neuroendocrine midgut tumors compared with placebo (27). Subsequently, the CLARINET study evaluated the anti-proliferative activity of lanreotide Autogel 120 mg monthly vs. placebo in patients with advanced, well or moderately differentiated (Ki67< 10%) NET arising from midgut, pancreas, and hindgut as well as of unknown primary site with or without disease progression. The CLARINET study showed that lanreotide Autogel was associated with prolonged progression-free survival (PFS) compared to placebo (median not reached vs. median 18 months, P<0.001) (29). More recently, long-term results of both studies have become available. The follow-up study of PROMID provides data of long-term survival. The median overall survival was only slightly different in patients treated with octreotide or placebo (84.7 and 83.7 months) [HR = 0.83 (95% CI:0.47–1.46); p = 0.51], though crossover of the majority of placebo patients to octreotide LAR may have hampered the data (30). The CLARINET

open-label extension (OLE) study reported long-term safety and additional efficacy data in patients with metastatic G1 G2 non-functioning pancreatic, midgut or unknown primary NET. Patients with stable disease (SD) at core study end, who were treated either with lanreotide or placebo or PD (placebo only), continued or switched to lanreotide in the OLE. Patients continuing lanreotide reported fewer adverse events during OLE than core study, and patients switched to lanreotide reported similar adverse events rates in OLE and core studies, except more diarrhea. Median lanreotide PFS was 32.8 months (95% CI: 30.9, 68.0). Thus, this OLE study suggests that long-term treatment with lanreotide Autogel 120 mg maintained favourable safety and tolerability, and data also provide new evidence of lanreotide anti-tumor efficacy (30).

Currently, as reported in the most reliable and widespread international guidelines (ENETS, NCCN), long-acting SSA octreotide and lanreotide are considered as a keystone of therapy, both due to their direct inhibitory effect on tumor hormone production and antiproliferative activity, with minimal adverse effects (31, 32). The most common adverse events include abdominal pain with cramps, constipation, diarrhea, steatorrhea, injection site irritation and local pain, nausea and vomiting. Less frequent adverse events are hypothyroidism and cholecystitis. Acute pancreatitis, alopecia, acute hepatitis, hyperbilirubinemia, hyperglycemia, hypoglycemia, prolonged QT interval and arrhythmias are rare but still possible complications (33). A relevant adverse effect is the development of gallstones, in up to 60% of patients, deriving from inhibition of cholecystokinin release which in postprandial induces emptying of the gallbladder (34).

The treatment with long-acting preparations of standard dose SSA consists in an intramuscular injection of octreotide-LAR 30 mg or lanreotide Autogel 120 mg every 4 weeks. Nevertheless, there has been a general trend supporting the use of high doses of octreotide LAR or lanreotide Autogel to control symptoms and tumor progression in patients with NEN, after progression under standard SSA dose (35). A study using biopsy specimens taken before and during SSA using low and high doses, showed that apoptosis in NET was induced only by high dose SSA (36). Furthermore, a substantial number of NET patients escape from treatment within months and the potential mechanisms involved in desensitization to SSA, yet largely unknown, include down-regulation of SSTR as well as the outgrowth of clones lacking the expression of SSTR, which the currently available SSA bind with high affinity (37). Nonetheless, there is evidence suggesting that in some patients escape could be overcome by increasing the dosage of SSA. Some studies suggested that the antiproliferative effect of SSA could be dose-dependent in progressive or metastatic NET (36, 38-41). The effect of shortened interval of octreotide LAR was prospectively investigated in a series of 28 well or

moderately differentiated NET with promising results (42). Octreotide LAR 30 mg administered every 21 days in well differentiated NET with progressive disease at standard-dose interval, resulted in complete and partial control of clinical symptoms in 40% and 60% of cases, respectively. Circulating neuroendocrine markers were significantly decreased in 30% of cases. A stabilization of disease was obtained in 93% and objective response in 7%. The median time to progression (TTP) was significantly longer by using the shortened interval of LAR administration as compared to the standard one (30 vs 9 months, p<0.0001). Furthermore, data derived from retrospective studies as well as from few prospective trials, generally support the switch to high dose SSA in patients with disease progression and/or uncontrolled symptoms (43-45), thus increasing SSA dose or shortening the dosing interval have become common clinical practice.

However, to date, systematic prospective trials evaluating safety and efficacy of high dose SSA in NET are still lacking, and experience is largely borrowed from high dose schedules in acromegaly (46, 47).

Aim of the study

The primary objective of this study was to evaluate the efficacy of two different high-dose SSA schedules (octreotide LAR 60 mg administered every 28 days and lanreotide Autogel 120 mg administered every 21 days) in NET patients with progressive disease under standard SSA dose for at least 6 months.

Secondary aims were the evaluation of the objective response rate (ORR), the clinical response and the biochemical response, together with safety assessment.

Patients and methods

This is a phase 2, single center, prospective, open label study. The study population consisted of 20 consecutive patients, 14 males (70%) and 6 females (30%), mean age 54.2 ± 14.7 years (range 22-84 years) enrolled among patients with NET in follow-up at the Unit of Neuroendocrine Tumors, Department of Clinical Medicine and Surgery, 'Federico II' University Hospital of Naples. The patient population included patients with histologically confirmed diagnosis of well or moderately differentiated NET (G1 or G2), as defined by the last WHO classification criteria for GEP NET, bronchial, and thymic origin (4, 5). Tumor stage was evaluated according to the last TNM classification (48). All included patients had tumor progression (either radiological or clinical) under a standard-dose treatment with SSA (Octreotide LAR 30 mg every 28 days or Lanreotide Autogel 120 mg every 28 days) for at least 6 months (mean 34.7 ± 38.8 months, range 6-119). Progressive disease was defined as increased tumor size according to the "Response evaluation criteria in solid tumors" (RECIST) definitions (49). Patients were enrolled in accordance with international standards of good clinical practice and written informed consent document was provided by patients or their legal representatives. To be eligible for the study, patients were required to be adult aged at least 18 years with histologically proven NET, and at least one lesion that could be accurately measured by spiral computed tomography scan. Subjects were excluded from participation if they had known hypersensitivity to SSA, prior or concomitant malignancies other than NET, unstable systemic diseases, pregnancy or breast-feeding, any active or uncontrolled infection/disorder, psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgement of the investigator would make the patient inappropriate for entry into this study.

Baseline characteristics of the patients are shown in Table 5. Twelve patients had sporadic NET (60%) and 8 patients had MEN1-related NET (40%). Primary tumor sites were mainly in the gastro-entero-pancreatic tract (10 pancreas, 5 ileum, 1 duodenum, 1 rectum), 2 bronchial. In one case, the primary tumor site was unknown. Ki67 index was available in all patients: 12 patients (60%) had Ki67 ≤ 2% (G1) and 8 patients (40%) had Ki67 3-20% (G2).

Metastases were diagnosed in 15 (75%) patients, mainly to the liver 13 (65%), and 2 (10%) patients had locoregional lymph node metastases. In 5 (25%) patients there was no evidence of local or distant metastases. Surgical resection of the primary tumor was performed in 8 (40%) patients before starting SSA. No other previous antitumor treatment was performed. All the included patients underwent functional assessment of SSTR positivity with either Octreoscan or 68GaPET before starting therapy with SSA. NET was non-functioning in 10 (50%) and functioning in 10 cases (50%). Among functioning NET there were 5 carcinoid syndromes, 4 Zollinger Ellison syndromes and 1 paraneoplastic acromegaly. At study entry, neuroendocrine markers and clinical symptoms were not controlled in 20 (71%) and 19 (68%) patients, respectively. At study entry, 9 of the 10 patients with functioning NET were receiving therapy with either loperamide or proton pump inhibitors, according to the specific symptoms. CgA was evaluated as aspecific neuroendocrine biochemical marker in every patient, while 24-h urinary 5-HIAA, serum gastrin and IGF-1 levels were determined in functioning NET as specific markers for carcinoid syndrome, Zollinger Ellison syndrome and paraneoplastic acromegaly, respectively. All patients presented with good performance status (ECOG grade 0 or 1).

The following therapeutic options with high dose SSA were evaluated: octreotide LAR 60 mg every 28 days and lanreotide Autogel 120 mg every 28 days. During high dose SSA therapy, patients maintained symptomatic treatments (loperamide, proton pump inhibitors) according to their symptoms. Patient enrollment started in November 2015, the mean follow-up was 29.9 ± 4.6 months (range 20-35). High dose SSA was started after disease progression with SSA at standard dose: radiological in 17 patients, clinical in 2, both radiological and clinical in 1 patient. Study duration was 36 months, including screening, treatment and follow-up.

Efficacy

Efficacy was evaluated by median PFS (mPFS), objective response rate (ORR), clinical and biochemical response. Radiological, clinical and biochemical data were recorded for every patient before starting high dose SSA treatment and every 3-6 months during follow-up. PFS was defined as the time from first study drug administration (high dose SSA) to objective tumor progression. If a patient had not had an event, PFS was censored at the date of last adequate tumor assessment.

ORR evaluation included complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) evaluated by contrast enhanced computed tomography (CT) or magnetic

resonance imaging (MRI), according to the RECIST1.1 criteria, using the same technique at baseline and during follow-up.

Biochemical response was evaluated by neuroendocrine marker (one or more), if abnormally increased before starting high dose SSA treatment. CR was defined as normalization of neuroendocrine marker, PR as reduction ≥ 50% in at least one marker, no response as variation <50%, progression as increase ≥ 50%.

Clinical evaluation was based on symptom referred at baseline and during follow-up, using an analogical scale (score range 0-3: 0 no symptoms, 1 mild, 2 moderate, 3 severe). Both symptoms related to endocrine syndrome, such as flushing, diarrhea, and aspecific symptom, such as abdominal pain were evaluated. Complete response was defined as total regression of symptoms from whatever score to score 0, partial response was defined by symptom decrease of at least 1 point not reaching score 0.

The variations of symptomatic drugs dose (loperamide, proton pump inhibitor) during follow-up were also recorded.

Safety

Safety assessments included monitoring of adverse events and toxicity every 3-6 months during follow-up, through evaluation of vital signs, physical examinations, and regular monitoring of hematological and clinical biochemistry values as well as gallbladder ultrasonography study. We classified adverse events in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0.

Statistical analysis

The statistical analysis was performed using the SPSS package version 20 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean ± SD. Primary efficacy and safety analyses were conducted at end of study for all patients. PFS was analyzed graphically by using the Kaplan-Meier survival estimates.

Results

Tumor response

High dose SSA was administered for a mean follow-up of 29.9 ± 4.6 months (range 20-35). Ten (50%) patients were treated with octreotide LAR 60 mg every 28 days and 10 (50%) patients with lanreotide Autogel 120 mg every 21 days. During high dose SSA administration no other concomitant tumor-directed therapies were recorded.

The mPFS was not reached. Antitumor efficacy of high dose SSA was evident in 16 (80%) patients. Partial ORR was recorded in 1 (5%) patient, stabilization in 15 (75%) and progression in 4 (20%). Treatment with octreotide LAR 60 mg/28d resulted in SD in 7 and PD in 3 patients. Treatment with lanreotide Autogel 120 mg/21d resulted in 1 ORR, 8 SD and 1 PD. The ORR was recorded in a patient with atypical bronchial carcinoid with liver metastases. There was no significant difference of mPFS according to type of SSA high dose schedule.

Biochemical response

Serum CgA levels were above the normal range at baseline in 16/20 (80%) patients. After high dose SSA, complete response was obtained in 3/16 (19%) and partial response in 9/16 (56%) patients. In 3/16 (19%) CgA levels remained persistently elevated and in 1/16 (6%) patients CgA levels increased. CgA remained within the normal levels in the 4/20 (20%) patients with normal basal CgA levels (Fig 1).

Basal u5-HIAA was elevated in 4/5 (80%) patients with carcinoid syndrome and after high dose SSA partial response was obtained in 3 (75%) and stable levels in 1 (25%) patient. The patients with carcinoid syndrome and normal basal u5-HIAA showed no significative variations of this parameter during follow-up.

Gastrin basal levels were elevated in all the 4 patients with Zollinger Ellison syndrome; after high dose SSA partial response was obtained in 2 (50%) patients and no response (persistently elevated) in 2 (50%) patients. In the patient with paraneoplastic acromegalic syndrome, IGF1 levels remained persistently elevated.

Octreotide LAR 60 mg/28d resulted in complete biochemical response in 2 (20%), partial response in 6 (60%), no response in 1 (10%) and progression in 1 (10%) patient.

Lanreotide Autogel 120 mg/21d resulted in complete biochemical response in 1 (10%), partial response in 7 (70%) and no response in 2 (20%) patients.

Clinical response

Before starting high dose SSA, 12 (60%) patients presented clinical symptoms and 6 (30%) patients were asymptomatic. Among the 12 symptomatic patients, complete response was obtained in 1 (8%), partial response in 6 (50%), no response in 4 (34%) and worsening of symptoms in 1 (8%). The 6 (40%) asymptomatic patients did not develop clinical symptoms during follow-up.

Octreotide LAR 60 mg/28d resulted in partial response in 4 and no response in 4.

Lanreotide Autogel 120 mg/21d resulted in complete clinical response in 1, partial response in 2 and worsening in 1 patient.

Among the most frequent symptoms, after high dose SSA, abdominal pain reported in 8 patients, completely disappeared in 1 patient, improved in 5 and persisted in 2; diarrhea, reported in 4 patients, partially disappeared in 3 and persisted in 1; flushing, reported in 4 patients, improved in 2 and remained stable in 2 (Table 6).

Safety

No treatment-related death was reported. High dose SSA were safe and well tolerated, no therapy withdrawal was recorded. In 4 (20%) patients asymptomatic cholelithiasis was diagnosed and treated with medical therapy. No other treatment-related adverse events were recorded.

Discussion

Synthetic SSA, octreotide and lanreotide, represent the first-line therapy in patients with functioning NET due to their ability to control hormonal hypersecretion (31, 32). Although SSA have been developed as anti-hypersecretory agents, their antiproliferative efficacy in NET is now supported by clinical trials, PROMID and CLARINET, for octreotide and lanreotide, respectively (27, 28). Furthermore, epidemiological data suggest the beneficial effects of SSA in terms of survival (3). Nevertheless, some patients escape from treatment, thus dose escalation of SSA has gradually become relatively common in clinical practice to overcome tachyphylaxis, and different hypotheses have been formulated to explain the reduction of efficacy of standard dose SSA in controlling both hormonal hypersecretion and tumor proliferation. Experimental data point out that tachyphylaxis could be related to the desensitization or internalization of somatostatin receptors as well as to the outgrowth of clones of tumor cells that lack somatostatin receptors. Dose escalation of SSA can be useful even in case of development of antibodies against SSA, injection site granulomas altering drug absorption, and heterogeneity in the expression of somatostatin receptor subtypes (37). Intratumoral heterogeneity may support the maintenance of SSA therapy beyond disease progression. Since not all tumor components become refractory simultaneously, SSA withdrawal may even worsen endocrine symptoms or lead to growth of stable lesions (50). An increase in the ORR has been initially demonstrated in acromegalic patient with high dose octreotide LAR (46, 47) as well as in NET with short acting SSA (38-41). Published data on the use of high dose long acting SSA are scattered and some retrospective reviews have analyzed the clinical employment of high dose SSA in NET. Nevertheless, prospective assessment of efficacy and tolerability of this common practice are scarce and there were no specifically designed clinical trials to explore high dose SSA. The present study prospectively evaluates the efficacy and safety of treatment with high dose of both commercially available SSA, octreotide and lanreotide, in patients with well or moderately differentiated, progressive NET of different origin. Two different schedules of high dose SSA were analyzed in patients with either symptomatic or radiological progression.

The efficacy and safety of above dose octreotide LAR regimens were previously investigated in a review including 17 studies, varying in designs, subjects, octreotide-LAR regimens, and definition of

outcomes. It emerged that higher doses of octreotide LAR were used to control both symptoms and tumor progression, reporting efficacy and no evidence of increased toxicity (44).

Our data highlight the effectiveness of high dose SSA therapy in progressive NET under standard SSA dose, either functioning or non-functioning. Median PFS was not reached and it can be related both to the relatively indolent behavior of the disease and to the duration of the study. In our series high dose SSA have demonstrated clinical efficacy in 80% of patients. Though the evaluation of therapeutic efficacy in NET is quite difficult due to their relatively indolent biological behavior, ORR has been obtained in 5%, while 75% of patients had stabilization of disease. Taking into account the advanced stage of disease in the majority of patients (65% stage IV) and the documented radiological progression during standard dose SSA in 18 out of 20 patients, we can already consider tumor stabilization as an effect of the antiproliferative activity of high dose SSA.

Besides antiproliferative activity, high dose SSA therapy showed even biochemical and clinical effectiveness. In the 80% of cases with elevated basal CgA, complete response and partial response were obtained in 19% and 56%, respectively. Moreover, considering the specific markers evaluated for the different syndromes, partial response was obtained in 80% of carcinoid syndromes and in 50% of Zollinger Ellison Syndromes. Although tumor marker levels may not be an accurate assessment of therapeutic efficacy, reduction in serum markers is frequently observed with high dose SSA (42, 51).

In this study symptom score improved in 58% of symptomatic patients, although this aspect is difficult to evaluate due to patient self-assessment. Improvement of symptoms has already been reported with high dose octreotide in a review specifically addressing the relationship between octreotide dose escalation and symptoms control in NET. In this retrospective chart review including nonresectable metastatic NET patients who received a dose greater than 30 mg intramuscular octreotide LAR, dose escalation of octreotide LAR was associated with improvement of diarrhea, flushing, bronchoconstriction and abdominal pain in NET patients who were refractory to the standard dose SSA (51).

In a recent systematic review, which included 18 studies and 1002 patients to systematically determine the efficacy and safety of escalated-dose SSA in clinical practice, disease control rates ranged from 30 to 100%, while response rates were modest (0-14%). Rates of biochemical improvement (27-100%) and symptoms improvement (23-100%) ranged widely depending on the population studied and the definition of response (52). There are now evidences that escalated dose SSA are well-tolerated in patients with GEP NET, with significant rates of disease control but low

rates of tumor response, and these recent data are consistent with the result of our prospective study.

The analysis of safety profile of high dose SSA in our series was consistent with the pharmacology of the class, and no unexpected or unreported adverse events occurred. Treatment was never withdrawn, and adverse events included only asymptomatic cholelithiasis, which only required medical therapy. Specifically, cholelithiasis, as in most NET patients, seldom requires surgery and seems to be related more to treatment duration than to the dosage of SSA (53). A multicenter, prospective, open label, single arm phase II study with Lanreotide Autogel 180 mg/28 days for 12 months in 35 patients with progressive NET under standard SSA dose, explored safety as primary endpoint and 2 treatment-related serious adverse events were reported, thus supporting substantial safety of treatment (54).

In this study the efficacy of high dose SSA therapy has been demonstrated radiologically, clinically and biochemically. Nevertheless, the small sample size and the short follow-up of this study did not allow to find any correlation among sex, site of primary NET, functional status, and response to high dose SSA in terms of PFS and TTP. Nevertheless, our data suggest that high dose SSA are effective in NET of different origin, progressive under standard dose SSA, functioning or nonfunctioning, and show good safety profile. Data from systematic prospective trials specifically designed to evaluate the safety and efficacy of high dose schedules in NET are still lacking, nevertheless recent trials such as NETTER-1 already consider high dose SSA to be the standard control arm after progression (55). Furthermore, international guidelines have recently updated their algorithms including high dose SSA among the therapeutic options in patients with progressive NET (12, 56). The efficacy of high dose SSA could allow to delay the need of other systemic or invasive locoregional therapies, which are associated with higher morbidity and toxicity than SSA. Further prospective, randomized studies, with large number of patients and longer duration of follow-up are required to understand if our preliminary data would translate into a real survival advantage as well as to identify the most effective option among high dose SSA schedules, possible predictors for response and the amount of delay of other more toxic treatments.

Tables and figures

Table 1. WHO classification of gastroenteropancreatic neuroendocrine neoplasms (NEN)

	Ki 67 (%)	Mitotic index (x HPF[1])
Well Differentiated NEN		
Neuroendocrine tumor (NET) G1	≤ 2	< 2/10
Neuroendocrine tumor (NET) G2	3-20	2-20/10
Poorly Differentiated NEN		
Neuroendocrine carcinoma (NEC) G3	> 20	> 20/10

[1]HPF, High Power Field

Table 2. WHO Classification of pulmonary neuroendocrine neoplasms

	Typical Carcinoid	Atypical Carcinoid	Large Cell Neuroendocrine Carcinoma	Small Cell Carcinoma
Mitoses per 2 mm²	0-1	2-10	> 20 (median 70)	> 10 (median 80)
Necrosis	No	Focal, if any	Yes	Yes

Table 3. Functioning neuroendocrine neoplasms

	Signs/ symptoms	Secreted peptide(s)	Primary site	Biochemical marker(s)
Carcinoid Syndrome	Flushing, diarrhea, abdominal pain, bronchoconstriction, tricuspid and pulmonic valve regurgitation	Serotonin Tachykinins, Neurokinins	Jejunum / ileum (pancreas, lung, rectum)	u5-HIAA[1], CgA[2], NTproBNP[3]
Insulinoma	Hypoglycemia and rapid improvement after glucose (Whipples' triad)	Insulin	Pancreas	72-h fasting test (Plasma glucose, Insulin, C-peptide, ß-hydroxybutyrate)
Zollinger-Ellison-Syndrome (Gastrinoma)	Severe peptic ulcer disease, gastroesophageal reflux, diarrhea	Gastrin	Duodenum (70%) pancreas (25%); other sites (5%)	Fasting serum gastrin, gastric pH secretin-stimulation test
VIPoma (Werner Morrison Syndrome; WDHA[4])	Watery diarrhea, hypokalemia, achlorhydria/ acidosis	Vasoactive intestinal peptide (VIP)	Pancreas > 90%	Plasma VIP
Glucagonoma	Diabetes, necrolytic migratory erythema, weight loss, nausea	Glucagon	Pancreas	Serum glucagon

[1]u5-HIAA, urinary 5-hydroxyindoleacetic acid; [2]CgA, Chromogranin A; [3]NTproBNP, N-terminal pro b-type natriuretic peptide; [4]WDHA, watery diarrhea, hypokaliemia, achlorhydria/acidosis

Table 4. Biomarkers in NET

Biomarker	Site of primary tumor	Sensitivity	Specificity
Chromogranin A	All sites	43-100%	10-96%
u5-HIAA[1]	Midgut	35%	Up to 100%
Gastrin	Stomach, duodenum, pancreas	Up to 100%	<20%
Insulin	Pancreas	Up to 100%	<20%
Pancreatic polypeptide	Pancreas, midgut	31-63%	Up to 67%

[1]u5-HIAA, urinary 5-hydroxyindoleacetic acid

Table 5. Patients' characteristics

Parameter	Number of patients (%)
Patients	20
Male/female	14 (70) /6 (30)
Sporadic/MEN1-associated NET	12 (60) / 8 (40)
Site of primary tumor	
Pancreas	10 (50)
Ileum	5 (25)
Duodenum	1 (5)
Rectum	1 (5)
Bronchial	2 (10)
Unknown primary	1 (5)
Grading	
G1	12 (60)
G2	8 (40)
Ki67 (%)	
≤ 2	12 (60)
3-20	8 (40)
Staging	
Primary tumor without metastases	5 (25)
Locoregional lymph nodes	2 (10)
Liver metastases	13 (65)
Prior surgery	8 (40)
Octreoscan positivity	9 (45)
^{68}GaPET positivity	11 (55)
Non-functioning NET	10 (50)
Functioning NET	10 (50)
Zollinger Ellison syndrome	4 (40)
Carcinoid syndrome	5 (50)
Acromegaly	1 (10)

Table 6. Clinical response during high dose SSA therapy

Symptom	Patients	Complete response	Partial response	No response	Progression
Abdominal pain	8	1	5	2	0
Diarrhea	4	0	3	1	0
Flushing	4	0	2	2	0
Dyspnea	2	0	1	1	0
Cough	2	0	1	1	0
Pyrosis	4	1	3	0	0

Figure 1. Biochemical response in 16/20 patients with Cromogranin A (CgA) levels above the normal range at baseline: complete response (CR) was obtained in 3/16 (19%) and partial response (PR) in 9/16 (56%) patients. In 3/16 (19%) CgA levels remained persistently elevated (NR, no response) and in 1/16 (6%) patients CgA levels increased (PD, progressive disease)
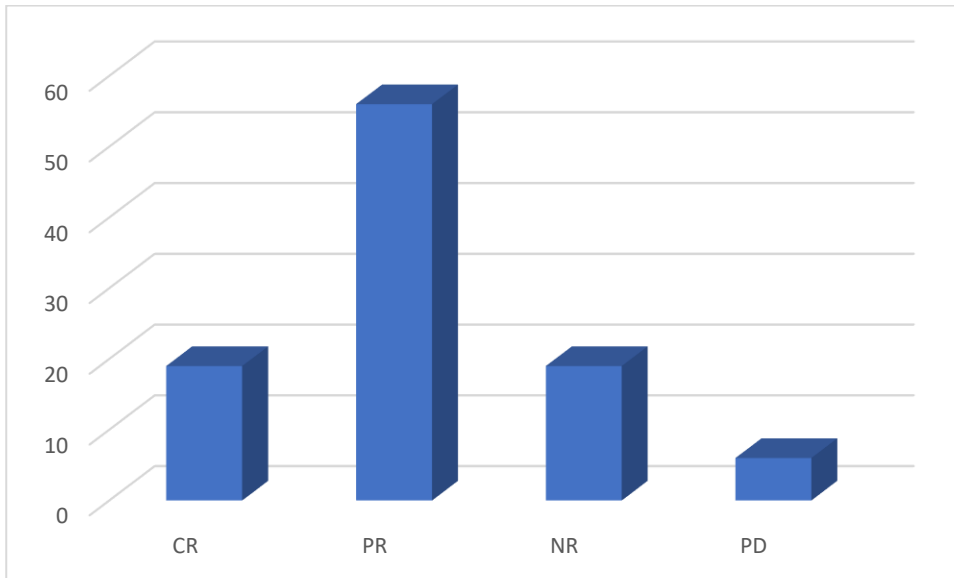
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