**Non-conventional doses of somatostatin analogs in patients with progressing well differentiated neuroendocrine tumor.**

**Short title:** Non-conventional doses somatostatin analogs in NET

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**Abstract 250 ws**

*Purpose*

To evaluate antiproliferative activity and safety of non-conventional doses of somatostatin analogs (HD-SSA) in patients with well-differentiated gastro-entero-pancreatic (GEP) neuroendocrine tumors (NET) patients with disease progression according to RECIST criteria on a previous treatment.

*Methods*

A retrospective analysis of prospectively maintained databases from 13 Italian NET-dedicated centers was performed. Main inclusion criteria were: well-differentiated G1 or G2 GEP-NET, treatment with HD-SSA (either with increased administered dose [dose intensity] or reduced administration interval [dose density]), progressing disease with a previous treatment before HD-SSA treatment. Main endpoints were progression-free survival (PFS) and safety.

*Results*

Of 198 patients, 140 matched inclusion criteria and were included in the analysis. Overall, median PFS was 31 months. Use of HD-SSA as second-line treatment was associated with reduced risk for progression or death compared to third or further line treatment (HR: 2.12, p= 0.004). There was no difference in PFS between HD-SSA by increased dose density or intensity. Partial response according to RECIST criteria was observed in 12 patients (8.6%) and 106 (75.7%) achieved stable disease.

Adverse events occurred in 21 patients (15.0%), 2 of whom had G3 biliary stone disease. No patients discontinued HD-SSA treatment due to adverse events.

*Conclusions*

HD-SSA is an active and safe treatment option in patients with progressing well-differentiated GEP-NET. The high rate of objective responses observed is worth prospective validation.

## Introduction

Neuroendocrine neoplasms (NEN) are a heterogenous class of tumors which are classified according to differentiation, proliferation, primary site and hormone production (1,2). While differentiation is defined according to morphological features, grading is defined according to the percentage of proliferating cells stained by MIB1 antibody (ki67). According to the most recent World Health Organization (WHO) classification, NEN are classified as grade 1 (G1), G2 or G3 if ki67 is <3%, 3-20% or over 20%. Well-differentiated NEN are commonly referred to as neuroendocrine tumors (NET),.

The mainstay of treatment of metastatic NET are somatostatin analogs (SSA), which are used to control both tumor proliferation and symptoms from hormone hypersecretion by the tumor. The two SSA approved for clinical use are lanreotide autogel 120 mg and octreotide long acting release (LAR) 30 mg. Each SSA is administered every 28 days and yielded longer progression-free survival than placebo in two phase III trials (3,4). Guidelines recommends treatment with SSA over chemotherapy for advanced NET unless tumors do not show some worrisome features such as rapid progression (<6-12 months), high tumor burden, mass-effect symptoms and/or higher proliferation index (5,6).

Since SSA are usually well-tolerated, being gallstone disease the only potentially severe adverse event (AE, ref. 7), modified schedules in an attempt to deliver higher doses of SSA have been used. Higher doses of SSA (HD-SSA), also referred to as non-conventional SSA doses, are achieved by either increasing administered dose (increased dose intensity; e.g. octreotide LAR 60 mg) or by reducing interval between administrations (increased dose density; e.g. lanreotide autogel 120 mg every 21 or 14 days). This approach is routinely used in acromegalic patients and, similarly, to achieve symptoms control in patients with hormone-producing NET who failed on standard-dose SSA (SD-SSA).

Although used in daily clinical practice, evidence about HD-SSA use for disease control is scarce so that guidelines suggest rather than recommend its use for this indication (5).

We present results of a multicenter Italian study of HD-SSA prescribed to pursue disease control in patients with gastro-entero-pancreatic NET (GEP) with radiological disease progression according to the Response Evaluation Criteria in Solid Tumors (RECIST, ref. 8) on a previous treatment.

**Methods**

*Study design*

All consecutive NET patients starting SSA treatment at non-conventional doses at 13 Italian dedicated centers from January 2004 to December 2017 were collected. According to ENETS Center of Excellence requirements, all NET patients clinical data were prospectively collected at the referral Center and then retrospectively aggregated in a single computerized data sheet.

Study inclusion criteria were: histological diagnosis of sporadic well differentiated GEP-NET (G1-G2), evidence of progressive disease per RECIST version 1.1 (8) before HD-SSA start on the previous line of treatment, treatment with HD-SSA.

For the purpose of this study, HD-SSA treatment has been defined either as increased dose intensity (lanreotide 180 mg or octreotide LAR 60 mg every 28 days) or increased dose density (lanreotide 120 mg or octreotide LAR 30 mg every 14 or 21 days). Previous treatment with SSA at standard doses was required. Patients treated with HD-SSA to achieve symptom control but with no evidence of radiological PD per RECIST criteria were excluded.

The following baseline characteristics have been collected: gender, age at the time of HD-SSA start, primary NET site, WHO 2010 classification, grade, presence of symptoms related to hormone hypersecretion, surgery of primary tumor, HD-SSA treatment characteristics (type of SSA, dose, frequency of administration, duration of treatment) and previous lines of treatment.

Study was closed in December 2018. Patients were followed up until treatment withdrawal, PD per RECIST criteria or death.

The histological specimens were examined by a NET-dedicated pathologist at each Center. Tumors

were classified according to the WHO 2010 classification and the ENETS grading system (1,2). Ki-67 proliferation index was expressed as a percentage based on the count of ki67-positive cells on 2,000 tumor cells in the areas of the highest immunostaining.

Disease assessment with clinical and radiological work-up has been conducted according to most recent ENETS guidelines (5,9–11). Disease response was evaluated according to RECIST criteria (8). Objective response rate (ORR) was defined as the proportion of patients who achieved complete response (CR) or partial response (PR) as better response during therapy.

All patients or their legal representatives provided written informed consent for SSA treatment and for anonymous review of their data for research purpose. The study protocol was approved by local Institution Review Board (Comitato Etico Indipendente, S.Orsola-Malpighi University Hospital, Bologna) and was conducted in accordance with the principles of the Declaration of Helsinki ($6^{th}$ revision, 2008).

*Statistical analysis*

Categorical variables were expressed as numbers (percentage). Continuous variables were reported as median and range. Progression-free survival (PFS) was defined as the interval between the start of the therapy and the time of progression of disease (PD). PFS was measured using the Kaplan-Meier method and the results were compared using the log-rank test. Predictive risk factors for PD were evaluated by univariate and multivariate analysis using the Cox proportional hazards method. Risk factors were expressed as hazard ratios (HR) [95% confidence interval (CI)]. The multivariate model was designed using the forward stepwise method after including all variables. All analyses carried out for predictive and risk factors are listed in the tables. The *p* value was considered significant when inferior to 0.05. Statistical analysis was performed using a dedicated software (IBM – SPSS Statistics v. 22).

## Results

*Study population.*

In 198 patients treated with HD-SSA for advanced NET, 46 patients with missing data and 12 patients with thoracic primary NET have been excluded from the analysis. Baseline characteristics of 140 evaluated patients were summarized in Table 1.

Eighty-four patients (60.0%) were male. Median age at SSA start was 65 years (range 29-87). Primary tumor site was gastrointestinal (GI) tract in 97 patients (69.3%) and pancreas in 43 (30.7%). As for WHO classification, 75 patients (53.6%) had a NET G1, 63 (45.0%) a NET G2; data was missing in 2 cases (1.4%).

Forty-seven patients (33.6%) had symptoms related to hormone hypersecretion (such as carcinoid syndrome, hyperinsulinemic hypoglycaemia, Zollinger-Ellison syndrome).

Primary tumor surgery was performed in 90 patients (64.3%).

As for SSA treatment, 7 patients (5.0%) received treatment at increased dose intensity, while 133 (95.0%) were treated with a dose density increase. Ninety-five patients (67.9%) received HD-SSA as second-line treatment, while 45 patients (32.1%) as third or further line.

Median duration of treatment with HD-SSA was 16 months (range: 1-106).

*Progression Free Survival (PFS)*.

Median PFS was 31.0 months (95% CI 19.3-42.6; Figure 1). Significantly longer PFS was associated with second-line HD-SSA (57 months, 95%CI 9.4 – 104.6) compared to third or further lines (22 months, 95%CI 13.0 – 31.0; p = 0.007) (Figure 2).

No significant differences in PFS according to gender (median in male: 25 months, female: 33 months; p=0.848), type of non-conventional dose SSA (median in increased dose intensity: 17 months, increased dose density: 33 months; p=0.078), primary tumor site (median in GI: 27 months, pancreas: 34 months; p=0.745), primary tumor surgery (median resected primary: 39 months, not resected

primary: 24 months; p=0.471), WHO 2010 classification (median in G1: 33 months, G2: 25 months; p=0.431), presence of hormone hypersecretion syndrome (median in patients with syndrome: 33 months, without syndrome: 23 months; p=0.205) were observed.

Risk factors for PFS were reported in Table 2. A higher risk for progression or death was associated with the use of HD-SSA as third or further line of treatment compared to second line on univariate analysis (HR 1.95, 95% CI 1.18-3.22; p=0.009), while gender, primary site, grading, presence of symptoms related to hormone hypersecretion, resection of primary tumor, type of HD- SSA (increased dose density vs increased dose intensity) were not.

At multivariate analysis, the association of use of HD-SSA as third or further line was independently associated with a higher risk for progression or death (HR 2.12, 95% CI 1.28-3.51; p=0.004) (Table 2).

Disease-control rate was 84.3%: 12 patients (8.6%) achieved partial response according to RECIST criteria and 106 (75.7%) stable disease; no complete response was observed.

*Safety*

Adverse events were observed in 21 patients (15.0%): 16 patients presented with G1 diarrhea, 3 with G1 fatigue and 2 with G3 biliary stone disease. No patients interrupted SSA treatment due to occurrence of adverse events.

**Discussion**

In our multicenter Italian study, HD-SSA showed an interesting activity profile yielding a mPFS of 31 months (95%CI 19.3 – 42.6) when administered after radiological PD to previous SD-SSA in well-differentiated GEP-NETs. Moreover, earlier HD-SSA administration was associated with greater PFS benefit (HR: 2.12 for HD-SSA administered from third line onwards, 95%CI 1.28 – 3.51; p=0.004), while no significant difference was observed whether HD-SSA was achieved by increasing dose intensity or dose density.

SSA are routinely used as first-line treatment for advanced well-differentiated NET, especially for G1 and low-G2 ones (5). Their use is aimed to tumor growth control, as well as symptoms control in syndromic patients. Their antiproliferative effect has been clinically proved by two large phase III randomized studies in both GI-NET (3) and GEP-NET (4): longer PFS in respect to placebo was observed with lanreotide LAR 120 mg every 28 days (not reached vs. 18.0 months, HR: 0.47 95%CI 0.30-0.73, P<0.001) and Octreotide 30 mg every 30 days (14.3 vs 6 months HR: 0.34 95%CI 0.20-0.59, P=0.000072), respectively. No objective response was observed in these trials.

Increased dose density or intensity of SSA is commonly used in clinical practice, mainly to achieve symptoms control in syndromic patients.

Since G1 and low-G2 NETs are in most cases characterized by a slow growth even after PD, chemotherapy should be delayed in absence of compelling worrisome features (5,6), in order to preserve quality of life. Tyrosine-kinase inhibitors, however, have a not-negligible toxicity profile which affects patients' quality of life (12,13).

ENETS guidelines mention the use of increased dose density or intensity SSA regimens at PD after SD-SSA (5), without clear recommendation because of scarce evidence quality (14–18).

In the single-arm phase II prospective "HIDONET" study, 28 patients (21 GEP, 6 thoracic, 1 unknown primary) with locally advanced or metastatic well-differentiated NET received octreotide LAR 30 mg every 21 days (15). All enrolled patients had had tumor progression during therapy with Octreotide LAR 30 mg every 28 days. An ORR of 7% was observed thanks to the occurrence of two partial responses, while mPFS was 30 months (95%CI 24.7 – 35.3). Reported adverse events were diarrhea, pyrexia and abdominal pain (1 event each) and cholelithiasis (2 events). These results are consistent with and confirmed by our study which has a greater sample size, although retrospective. In fact, mPFS and ORR in our series were 31 months (95%CI 19.3 – 42.6) and 8.6%, respectively. However, no trial formally confirmed octreotide 30 mg every 21 days indication in progressing NET.

More recently, in the control arm of the randomized phase III NETTER-1 trial, 113 midgut NET patients received octreotide LAR 60 mg every 28 days after their tumor progressed to SD-SSA (19). After a median follow-up of 14 months, a mPFS of 8.4 months (95%CI 5.8 – 9.1) and a 3% ORR were observed. At 2018 annual American Society of Clinical Oncology (ASCO) meeting, the first update from the study reported an OS of 27.4 months in the high-dose octreotide arm (20). This result might appear different from ours, but some points should be considered. In this trial, all patients in the control arm received HD-SSA by increased dose intensity, while the same strategy was adopted in only 5% of patients in our series. In these patients, median PFS is 17 months, but is estimated from data from a small sample size (N=7). In addition, overall disease characteristics in the control arm from the NETTER-1 trial were consistent with a moderately aggressive disease, as showed by the early drop of Kaplan Meier estimates for progression-free survival on HD-SSA (19). Lastly, at the time of first analysis, median follow-up was 14 months compared to 16 months in our series.

In our series, lack of correlation between PFS and grading or PFS and NET primary site could be of note. While the latter is consistent with previous series (15), the former lack of association can be due to the low proliferation index in our series (median ki67 2%, IQR 1-6), being high-end G2 tumors are low-represented. This possibly smothered the difference in survival and response to treatment between G1 and G2 NET or small bowel and pancreatic NET. Since Ki-67 behaves as a continuous biomarker, the wide range of proliferation index in the G2 category (3-20% ki67) makes this group of NET a heterogenous one. However, this population distribution is consistent with ENETS guidelines which recommend SSA in G1 and lower-G2 well-differentiated NET (5).

Finally, it is interesting to note that administration of HD-SSA as earlier line of treatment is associated with longer PFS than in later lines with mPFS of 57 months (95%CI 9.4 – 104.6) and 22 months (95%CI 13.0 – 31.0) for patients treated in second line and in third or subsequent lines, respectively (HR: 2.12 for third line onwards, 95%CI 1.28 – 3.51; p=0.004). This difference can be secondary to a progressive selection of more resistant and biologically aggressive clones by subsequent treatment lines or to a

selection bias: patients with better prognostic factors (smaller size of disease, limited or slow progression to SD-SSA) may be more likely to be treated with HD-SSA before any further treatment per clinical practice.

Of note, HD-SSA toxicity remains manageable, being cholecystitis the only potential warning AE (1.4% in our series)(7).

Limitations of our study are mainly its retrospective nature and potentially the lack of a systematic tumor reassessment at progression (by core biopsy or FDG-PET scan) to exclude tumor dedifferentiation towards more aggressive features (grading, ki67).

In conclusion, HD-SSA achieved through either increase in dose density or dose intensity can be a feasible option in a selected NET population, characterized by low proliferation index and limited or slow progression. To further clarify HD-SSA usefulness, a phase II study of Lanreotide Autogel 120 mg every 14 days in GEP-NET patients with their tumor progressing on Lanreotide Autogel 120 mg every 28 days is ongoing (NCT02651987).

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**Precis (200 chs, including spaces)**

Data on somatostatin analogs-pretreated neuroendocrine tumors treated with high-doses of somatostatin analogs upon progression were analyzed. High-dose somatostatin analogs use was active and safe.