Somatostatin Analogs in Patients with Zollinger Ellison Syndrome (ZES): An Observational Study

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Abstract

PURPOSE: Zollinger Ellison syndrome (ZES) is a rare syndrome caused by gastrin hypersecretion from a gastrinoma. Gastrinoma treatment has two goals: the control of the gastrin-excess state and the control of tumor growth. While therapy for the syndrome is univocally based on proton pump inhibitors, the one for disease control is still debated. We here aimed at evaluating the role of SSAs in the control of tumor progression in a series of ZES patients.

METHODS: A retrospective analysis of a prospectively collected database of ZES patients, followed and managed from 1990 to 2019, was performed. The patients' clinical, pathological, treatment, and follow-up data were analyzed. Data regarding SSAs therapy start, dosage, duration, and side effects were collected.

RESULTS: 33 patients with ZES were diagnosed. Fourteen patients (42%) had a G1 NEN, five had G2 (15%), none had G3. Fifteen patients (45%) had metastatic disease. Overall, 12 (36%) underwent SSAs therapy. The median treatment duration was 36 months. Eight patients (67%) had a sustained response to SSA, four (33%) showed an early progression, with a significant difference in terms of PFS between the two groups (84 vs 2 months, $p=0.004$). No differences in terms of OS and PFS were observed between the two groups, despite the proportion of metastatic patients was greater in the SSA-treated group (75% vs 29% in the non-treated group, $p=0.01$).

CONCLUSION: Present data support the use of SSAs in ZES, considering that gastrinoma is mainly a well-differentiated low-grade tumor (G1 or G2), with a high expression of somatostatin receptors.

Introduction

Gastrin secreting tumors, or gastrinomas, are rare functioning neuroendocrine neoplasms (NEN), usually arising from the duodenum or the pancreas. Gastrin hypersecretion from gastrinoma is responsible for Zollinger Ellison syndrome (ZES) characterized by hypersecretion of gastric acid and severe recurrent peptic disease [1]. Gastrinoma occurs in one to three cases per million people in the USA annually, making them the second most common functional, pancreatic neuroendocrine neoplasm [2]. Approximately 75% of gastrinomas are sporadic, while 25% of patients present with multiple endocrine neoplasia type 1 (MEN-1)[3].

There are two therapeutic goals in the management of patients with gastrinoma: the control of gastric acid hypersecretion and the treatment of the tumor itself. While the therapy for syndrome control is univocal and based on proton pump inhibitors (PPI), which have significantly decreased the morbidity and mortality resulting from severe ulcer disease [4], the management of the neoplastic disease is still debated.

Surgical treatment is the only curative approach for patients with gastrinoma, unfortunately, surgery is of limited value in presence of metastatic disease or multiple NEN in the context of MEN-1 [1]. In addition, in

up to 30% of cases, the primary tumor can not be precisely located [5].

Since 1980, long-acting somatostatin analogs (SSAs) have been used as a symptomatic treatment of well-differentiated functioning NENs. More recently, the PROMID and CLARINET phase III randomized trials demonstrated an increase of PFS in NEN patients treated with SSA [6, 7], even if in these studies only a few cases of gastrinoma were included.

However, based on these studies, the use of long-acting SSAs is currently recommended in all advanced NEN patients irrespective of the functional status [8]. Despite different case reports and case series suggested the role of SSAs on control of gastrin secretion and symptoms in ZES patients, as well as on tumor progression [9–12], to date only a few studies with a very low number of patients investigated specifically the role of SSAs in ZES [13].

We here aimed at evaluating the role of SSAs in the control of tumor progression in a series of consecutive enrolled ZES patients.

Methods

A retrospective analysis of a monocentric prospectively-collected database was performed on patients with ZES, followed and managed from 1990 to 2019, at the Division of Gastroenterology and Digestive Endoscopy at Fondazione IRCCS Ca' Granda, Ospedale Policlinico, Milan, Italy.

ZES syndrome was diagnosed based on clinical, biochemical, and imaging data. Each tumor has been retrospectively immunohistochemically classified according to the WHO 2010 classification based on Ki-67 index [14], when histological/cytological specimens were available, and the disease was staged based on the presence/absence of nodal or distant metastases, i.e. according to the current ENETS TNM clinical staging [15]. Other characteristics evaluated were the site and the size of the primary tumor and the number of lesions. Symptomatic, biochemical [circulating chromogranin A (CgA) and gastrin levels] and objective (tumor size) responses were evaluated according to the criteria of the Italian Trials in Medical Oncology (ITMO) group [16] and classified as complete or partial response (CR or PR), when facing with a decrease > 50%; the disease was classified as stable (SD), with a decrease of < 50% or an increase of < 25%; finally, the disease were classified as progressive (PD), in presence of an increase of more than 25%.

All the patients underwent a complete clinical, biochemical, and imaging evaluation at diagnosis and at regular intervals during follow-up. Plasma CgA levels and gastrin levels were prospectively collected at diagnosis, then after during the follow-up. The venous blood samples for gastrin and CgA assay were collected in EDTA-containing tubes between 8h00 and 10h00 a.m. after an overnight fast. The samples were centrifugated at a temperature of 4°C and the plasma was separated and stored at -30°C until assayed. CgA and gastrin were measured using commercially available kits. Imaging examinations, such as ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and functional nuclear medicine imaging (either Gallium-68 positron emission tomography (PET) or Octreoscan®) were collected at the diagnosis and then, during the follow-up. The rate of surgical interventions, the medical

regimen, the presence of associated diseases (including other malignancies), the presence of genetic syndrome, i.e. MEN-1, the cause of death, and the length of survival were also recorded.

The types of treatment were namely radical surgery, somatostatin analogs (SSAs), a combination of both, liver-directed therapies, or others (Peptide receptor radionuclide therapy (PRRT) or targeted-therapies).

Data regarding SSAs therapy start, dosage, duration, and side effects were collected. Finally, data on the median follow-up, overall survival (OS), and progression-free survival (PFS) were collected.

All data for each patient were anonymized after collection, recorded, evaluated, and analyzed.

The data collection was closed in November 2019.

Statistical analysis

Continuous variables were reported as median and range unless otherwise stated. Continuous data were analyzed using the non-parametric Mann-Whitney test. Kruskal-Wallis statistics followed by Dunn's multiple comparison test were used to compare variables repeated at different times.

Survival curves were estimated using the Kaplan-Meier method and the log-rank test was used for comparison of survival curves between groups of patients.

A p-value < 0.05, two-sided, was considered statistically significant.

The analyses were carried out by Graph Pad Prism version 6.00 (GraphPad Software, San Diego, California, USA), and MedCalc version 17.9.5 (MedCalc Software bvba, Ostend, Belgium).

Results

33 patients (18 female, median age 48 years, range 13–79) were diagnosed with ZES and managed from 1990 to 2019, at the Division of Gastroenterology and Digestive Endoscopy at Fondazione IRCCS Ca' Granda, Ospedale Policlinico, Milan, Italy

Diagnosis of ZES was based on clinical, biochemical, and histological parameters. Seventeen (52%) had a MEN-1 syndrome and 16 (48%) were sporadic. According to WHO 2010, 14 patients (42.5 %) had a G1 NEN, five had G2 (15%), none had G3, whereas, in 14 patients, grading was not available. Fifteen patients (45%) had metastatic disease at the diagnosis, and according to the ENETS TNM staging system, 14 patients (42.5%) was classified at stage I, 3 (9%) at stage II, 1 (3%) at stage III and the remaining 15 (45.5%) at stage IV as presenting distal metastases.

The most frequent primary localization was the pancreatic head in 14 patients (42.5%), followed by duodenal (30.3%), hepatic (6%), and nodal (3%) localization. In six cases (18.2%) primary neoplasm was occult. Patient characteristics are detailed in Table 1.

Table 1
Patient's demographic and clinical characteristics.

Characteristics	Total patient Number (N = 33)
Age in years, median (range)	48 (13–79)
Gender, M/F	15/18
MEN1, N (%)	17 (52)
Sporadic, N (%)	16 (48)
Location	
Pancreas, N (%)	14 (42.5)
Duodenum, N (%)	10 (30.3)
Liver, N (%)	2 (6)
Lymphnode, N (%)	1 (3)
Occult, N (%)	6 (18.2)
Grading:	
G1, N (%)	14 (42.5)
G2, N (%)	5 (15)
G3, N (%)	0 (0)
NA, N (%)	14 (42.5)
TNM staging at presentation	
Stage I, N (%)	14 (42.5)
Stage II, N (%)	3 (9)
Stage III, N (%)	1 (3)
Stage IV, N (%)	15 (45.5)
Outcome (alive/dead [†] /lost)	14/13/6
Gastrin levels, median (range)	532 (69-315000)
Treatment	
Radical surgery	9 (27.3)
SSAs therapy and non-radical surgery	6 (18.2)
SSAs therapy only	6 (18.2)
Other	

Among the 33 patients, 12 (36%) underwent SSAs therapy, due to metastatic disease in 10, and concomitant second neuroendocrine neoplasm in two. Six (18.2%) underwent SSAs therapy alone and six in combination with non-radical surgery. In the entire cohort of the patients, nine (27.3%) underwent radical surgery. Two patients underwent PRRT for disease progression to SSAs therapy.

The median treatment duration of SSAs treatment was 36 months (range 30–84). The biochemical response was documented in nine (75%) of the studied patients who achieved partial response in serum gastrin levels, presenting a decrease of more than 50% in serum gastrin levels [median value from 532 at baseline (range 709–1713) to 206 (median 253–1280)] after three months of treatment; in three patients no change had occurred and presented a rapid progression of the disease. During the prolonged follow-up, a long-lasting (36 months, range 30–84) biochemical response was observed. Complete clinical control (with no evidence of peptic disease and no upper gastrointestinal symptoms) was obtained in all but one patient, by concomitant PPI (omeprazole 60 mg/daily in 15 patients, esomeprazole 120 mg/daily in 8, rabeprazole 60 mg/daily in 10 patients).

Three patients (25%) had a sustained objective response to SSA, with clinical control and stable disease at imaging, whereas nine (75%) showed an objective progression of the disease, with a significant difference in terms of median progression-free survival (mPFS) between the two groups (= mPFS 84 months in responder group vs 2 months in the non-responder group, $p = 0.004$).

Overall, between SSAs treated and non-treated patients, no differences in terms of median OS and PFS were observed, despite the proportion of metastatic patients was greater in the SSA-treated group (75% vs 29% in the non-treated group, $p = 0.01$).

In the entire series, two patients had a type 2 gastric NEN (gNEN) diagnosed. In one case, gNEN was treated with endoscopic resection, in the other case SSA treatment was started with gNEN complete response at 12 months. No patients had gNEN diagnosed on SSA therapy.

No significant side effect development was observed in the 12 treated patients.

Discussion

The present study supports a role of SSA treatment in ZES patients, showing an excellent safety profile with a prolonged biochemical response in the majority of the patients treated with SSAs with a sustained objective response in 3/12 cases. A possible role of SSA in ZES treatment has been previously suggested due to the reported high expression of somatostatin receptors (SSTR) in gastrinoma [17–20]. In 2002, Kulaksiz et al. observed sstr2 expression in 100% of gastrinomas, while sstr3 and sstr5 were expressed in 79 and 76% of cases, respectively [17]. Accordingly, somatostatin receptor scintigraphy (SRS) has been known for years as the most sensitive technique for the detection of both primary tumors and metastatic disease in patients with gastrin secreting tumors [18–20]. More recently, the 68Gallium-PET

demonstrated a good detection rate in a series of 25 patients with ZES and negative CT findings [20]. In our series we observed a high rate of patients with positive functional imaging (88,5 %), confirming a high SSTR expression in ZES patients. Moreover, as previously reported in the literature [21], we observed most patients with gastrinoma having a grading G1 and G2 (42,5 and 15%, respectively), while no patients had G3 carcinoma. The inverse relationship between tumor grade and SSTRs expression is well known [21]. These observations represent a strong rationale for SSA therapy in gastrinoma.

In the last years, the use of PPI has dramatically improved the control of gastric acid hypersecretion, significantly reducing the morbidity and mortality of ZES related peptic disease. However, a portion of patients has been reported not to tolerate high doses of PPI or present symptoms of gastrin hypersecretion on PPI [22]. Since 1985, several case reports and small case series suggested SSA be effective in symptoms control in ZES patients. [11, 23–25], thus it is reasonable to think that SSA may further help obtain a complete clinical response. In this series, we observed a complete clinical control in all but one patient, with concomitant PPI therapy. SSA treatment thus could be of value in patients experiencing relevant side effects from PPI therapy or with a syndrome not completely controlled by PPIs alone even with dose escalation.

In our series, 12 of 33 ZES patients (36%) underwent SSAs therapy for a median treatment duration of 36 months (range 30–84). Overall, SSA treatment was well tolerated without significant side effects during the prolonged follow-up.

In 75% of cases, a reduction in gastrin levels of more than 50% was observed after 3 months of treatment compared with pre-treatment levels. In responder-patients, a long-lasting (36 months, range 30–84) biochemical response was observed in all cases. Similar results have been previously reported in ZES patients treated with octreotide (300 to 600 µg sc daily, in divided doses) with a reduction in gastrin levels ranging from 53 to 87% [11, 23, 26]. In most cases, the SSA effect on gastrin reduction was sustained for at least 12-months [11, 23, 26]. More recently, two studies on GEP-NET patients including ZES patients, suggested also long-acting SSA be effective in achieving a reduction in gastrin levels by $\geq 50\%$ [27, 28].

In addition, ZES patients are prone to develop gastric neuroendocrine tumor (gNEN), due to the trophic action of gastrin on ECL cell on the gastric body [29]. Interestingly, we observed the occurrence of gNEN in two of 21 cases in the group of patients non-taking SSA, while no gNEN were observed in the SSA-treated group. Since, the demonstrated effect of SSA on gastrin reduction in ZES patients, SSA therapy may have had a protective/therapeutic role on gNEN occurrence. Although the low incidence of gNEN does not allow to draw definitive conclusions, SSA could be of help in preventing gNEN occurrence or in treatment of multiple gNEN or recurrent disease.

A possible role of SSA therapy on tumor growth control and disease progression has been suggested by different studies [30]. However, studies focusing on ZES patients are scanty and heterogeneous, with a limited number of patients, moreover, their results are hardly comparable, because of the use of different SSA formulations and heterogeneous criteria to define response or progression of the disease. In 2002 Shojamanesh et al. reported the largest prospective study on ZES patients treated with SSA. A total of 15

consecutive patients with gastrinoma (three MEN-1) underwent octreotide treatment (initially 200 µg sc twice a day, since 1999 LAR formulation 20–30 mg in monthly) [31]. In all cases, progression over the 3 to 6 months before enrollment was documented. SSA treatment was continued until severe side effect development, complete disease remission, or significant progression. Tumor response was observed in 53% of patients (stabilization in seven and partial response in one patient) lasting 25 ± 6 months (range 5.5–54.1 months) [31]. In the present series, a sustained objective response to SSA was observed in 3/12 patients (25%) with an mPFS of 84 months, and a statistically significant difference between responder and non-responder ZES patients was observed $p = 0.004$. Interestingly, non-responder in most cases presented an aggressive course with early disease progression (mPFS 2 months), probably reflecting a more aggressive tumor behavior even before SSA treatment. On the other hand, the patients who showed an early response maintained it for a long period (mPFS of 84 months). Overall, we did not observe any significant differences in terms of median OS and PFS between SSAs treated and non-treated patients. This observation should not be interpreted as lack of efficacy of SSAs therapy, as in the SSA-treated group a significantly higher rate of metastatic patients was observed (75% vs 29%, $p = 0.01$). The occurrence of metastatic disease represents the most important prognostic factor in GEP-NEN and it is associated with a significantly reduced OS and PFS [32, 33]. Taking into consideration the observed comparable course of disease between SSAs treated and non-treated patients, even in presence of a significantly higher rate of metastatic disease in SSA treated patients, it could be postulated that SSA did actually have an impact on survival leveling up the two curves.

In conclusion, data from the present series suggest SSA to be safe and effective in obtaining a sustained reduction of gastrin secretion and a sustained objective response in 25% of cases. Further prospective studies are needed to clarify the impact of SSA treatment on survival in patients with ZES.

Declarations

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Conflicts of interest:

The authors declare no competing interests.

Availability of data and material:

not applicable.

Code availability:

not applicable.

Authors' contributions:

SM and MP planned the work; FC, AE, and MQ performed the literature search and collected the data in a dataset; SM analyzed the data; FC and SM wrote the first draft of the manuscript; FC, AM, and AE edited the subsequent versions of the manuscript; SM, MP, and PI critically revised the manuscript for relevant intellectual content. Finally, all authors read and approved the final manuscript.

Ethics approval:

This study was approved by the institutional review board and carried out in accordance with the approved guidelines.

Consent to participate:

not applicable.

Consent for publication:

not applicable.

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Figures

Figure 1

Flow chart diagram of the studied population