Clinical outcomes of patients with G1/G2 neuroendocrine tumors arising from foregut or hindgut treated with somatostatin analogs: a retrospective study

Title

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Abstract

Neuroendocrine tumors (NET) are rare tumors for which somatostatin analogs (SSA) are used not only for symptom control due to a functioning tumor, but also for the disease control of unresectable NET. The efficacy of SSA for midgut NET has been verified by previous studies, but insufficient evidence exists for SSA treatment of NET in the foregut and hindgut (F/H-NET). The aim of this retrospective study was to evaluate the efficacy of SSA for unresectable F/H-NET. Patients with unresectable F/H-NET treated with SSA between February 2011 and August 2017 at our hospital were retrospectively reviewed. Parameters of efficacy were progression-free survival (PFS), overall survival, objective response rate (ORR), and adverse events. Twelve cases with unresectable F/H-NET were extracted from our database. With a median follow-up time of 25.9 months, the median PFS was 13.6 months. Two- and 3-year survival rates were 87.5% and 62.5%, respectively. The ORR was 8.3%, and the disease control rate was 75%. Serious adverse events were not observed. Subgroup analysis, including G1/G2, and hepatic tumor load, which is the volume of NET liver metastases, did not reveal a difference in PFS. The efficacy and safety of SSA for F/H-NET seemed similar to that found in the PROMID study, highlighting its relevance for the treatment of this disease.

Keywords

Neuroendocrine tumor, somatostatin analog, foregut NET, hindgut NET, octoreotide, lanreotide

Introduction

Neuroendocrine tumors (NET) are rare malignancies that arise from the neuroendocrine system of the body. An epidemiological survey conducted in Japan in 2010 showed the incidence of new pancreatic and gastrointestinal NET (GI-NET) cases was 4.78 per 100,000 people [1]. Differences exist between Western countries and Japan with regard to the origin of GI-NET: midgut NET is common in Western countries while hindgut NET is common in Japan [2].

Somatostatin analogs (SSA) have been used to control not only symptoms caused by functioning tumors, but also the growth of unresectable NET. The efficacy of SSA for GI-NET was verified through PROMID [3] and CLARINET studies conducted mainly in Western countries [4]. However, the majority of enrolled patients with GI-NET in both studies had a midgut NET since foregut or hindgut NETs (F/H-NET) are rare in Western countries. To date, there has been little consensus or evidence on the use of SSA for the treatment of F/H-NET. Of a number of available guidelines on NET,

European Neuroendocrine Tumor Society (ENETS) 2016 consensus guidelines are the only ones to outline treatments for unresectable F/H-NET [5]. These guidelines recommend that SSA use may be considered in low-grade F/H-NET. However, almost no evidence exists to support this recommendation. We therefore explored the efficacy of SSA for patients with unresectable F/H-NET in this retrospective study.

Patients and methods

Methods:

We respectively reviewed patients with unresectable F/H-NET treated with SSA in our hospital between February 2011 and August 2017. The selection criteria were: (1) unresectable F/H-NET treated with SSA alone, and (2) grade 1 (G1) or 2 (G2) well-differentiated NET according to the 2010 WHO classification. The collected data included: age, gender, primary site, organ metastasis site, functional tumor or not, pathological findings, evaluation with somatostatin receptor scintigraphy or not, and hepatic tumor load (HTL), the latter having been regarded as a prognostic factor for progression-free survival (PFS) in previous studies [3] [4].

Statistical analysis

Efficacy parameters were PFS, overall survival (OS), and objective response rate (ORR). PFS was defined as the time from the date of initiation of SSA treatment to the date of the first progression or death (any causes), whichever came first, or was censored at the last date confirming PFS. OS was defined as the time from the date of initiation of SSA treatment to death (any causes) or was censored at the last date of confirmed survival. A survival curve was calculated by the Kaplan–Meier method. Survival time comparisons between groups in subgroup analysis were performed using a log-rank test. Statistical analyses were performed with EZR, which is a graphical user interface for R (The R Foundation for Statistical Computing, version 3.3.2) [6]. Tumor responses were assessed by computed tomography (CT) imaging according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. Adverse events were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The HTL was calculated using a method for integrating hepatic tumor and normal liver areas for each slice width (1 cm) by CT and calculating the proportion of total tumor volume to total liver volume. The cut-off of HTL was defined as 25% with reference to the CLARINET study [4].

Results

Patient characteristics

Thirty-two cases with unresectable NET were extracted from our database. Eighteen patients did not receive SSA treatment and two patients had a midgut NET. Therefore, 12 patents were enrolled in this study.

Ten of the 12 patients received SSA therapy as a first-line treatment and others as a second-line treatment (pre-treatments were investigational drugs including mammalian target of rapamycin [mTOR] and tyrosine kinase inhibitors. Details of SSA treatment were as follows: octreotide in eight patients, and lanreotide in four patients (enrolled in a domestic phase II trial) [7]. Ten patients had primary rectal tumors, one showed a stomach tumor, and one had a duodenal tumor. With regard to disease stage, four patients initially had metastatic disease, and eight had postoperative recurrent disease. All patients had liver metastasis. In terms of pathological grade, three patients had a G1 tumor and nine had a G2 tumor (Table 1).

Clinical outcomes

The median follow-up time was 25.9 months and the median PFS was 13.6 months (Fig. 1). For OS, 2- and 3-year survival rates were 87.5% and 62.5%, respectively. The ORR was 8.3% (1 of 12 patients), and the disease control rate was 75% (9 of 12 patients; Fig. 3). In a subset analysis for PFS according to the HTL, a significant difference in PFS was not noted; the median PFS was 16.5 months in patients with >25% of a HTL and 11.2 months in those with $\leq$25% of a HTL (Fig. 2). Differences between G1/G2 tumors, disease status (recurrence vs. initial metastatic disease), and number of metastatic organs other than liver (0 or $\geq$1; Fig. 2) were also not noted. Main adverse events were fatigue, constipation, diarrhea, pale stools, abdominal pain, injection site reactions and a decrease in platelets. All tumors were grade 1 or 2 and a serious adverse event was not observed (Table 2).

Discussion

To our knowledge, this is the first report of an investigation into the efficacy of SSA treatment for unresectable F/H-NET in Japanese patients. A retrospective study at a single institution described the survival of patients with hindgut NET using systemic therapies [8]. Several articles have highlighted clinicopathological factors associated with the occurrence and progression of hindgut NET [9][10].

The use of SSA for GI-NET is mentioned as set out below for each set of guidelines. National Comprehensive Cancer Network (NCCN) guidelines recommend SSA treatment for locoregionally advanced and/or unresectable non-functioning NET of

the gastrointestinal tract and pancreas by considering the disease status as following a symptomatic, clinically significant tumor burden, or clinically significant progressive disease. In comparison, European Neuroendocrine Tumor Society (ENETS) 2016 consensus guidelines recommend that SSA treatment should be selected according to the expression of primary organ and somatostatin receptors (SSTR). For F/H-NET, these guidelines also mention the following: “SSA use may be considered in low-grade NET of foregut or hindgut origin” [5]. Other guidelines, including NCCN guidelines and those of the Japan NeuroEndocrine Tumor Society (JNETS), do not have recommendations for the treatment of F/H-NET [11][12].

Our study revealed a median PFS of 13.6 months in unresectable F/H-NET treated with SSA. In terms of PFS, the PROMID study reported a median time to progression of 14.3 months while the CLARINET study reported the median PFS was not reached after 96 weeks at the time of publication. In our study, SSTR expression was not assessed. Therefore, we preferred to compare the results of this study with those of the PROMID study because all of the cases in the CLARINET study were SSTR positive. However, the Surveillance, Epidemiology and End Results (SEER) database reported metastatic F/H-NET had a worse prognosis than metastatic midgut NET [13]. Our study showed similar efficacy to the PROMID study in terms of PFS.

A phase II study of lanreotide for unresectable or metastatic well-differentiated NET in Japanese patients showed that the clinical benefit rate at 24 weeks as a primary endpoint was 64.3%, and median PFS as a secondary endpoint was 36.3 weeks [7]. In this phase II study, one patient with foregut (lung) NET and eight patients with hindgut NETs were included but an SSTR evaluation was not performed in all patients; however, a preferred outcome was observed. Data on foregut and hindgut NET from this study was limited.

In our study, a survival difference, in terms of PFS, between patients with a high and low HTL, or G1 and G2 tumors was not observed. In a subgroup analysis of the PROMID study, a survival difference between long-acting repeatable (LAR) octreotide and placebo groups was observed in a HTL $\leq$ 10% group, but not in a HTL >10% group. However, in the CLARINET study, a survival difference between lanreotide and placebo was observed in both HTL $\leq$25% and >25% groups for PFS, which means lanreotide may have a more favorable efficacy than LAR octreotide for SSRT-positive GI-NET, even in patients with a high tumor load. G2 tumors usually have a worse prognosis than G1 tumors in NET [13]. In the CLARINET study, a significant survival difference between patients with G1 and G2 tumors in terms of survival was also not observed. In the PROMID study, subgroup analysis according to

tumor grade was not implemented because most patients had a G1 tumor. The clinical impact of HTL and tumor grade on the prognosis of F/H-NET should be validated using a larger patient cohort because of the retrospective nature of this study and an analysis based on a small sample size.

Treatment results for F/H GI-NET are shown in a study of everolimus (RADIANT-4 study) [14]. Everolimus, an oral mTOR inhibitor, was observed to affect pancreatic NET [15]. The RAIANT-4 study was a phase Ⅲ study for advanced, progressive, well and moderately differentiated, nonfunctional NET with origin sites that included the lung, GI tract, or an unknown primary site. In the study, enrolled patients with F/H GI-NET comprised 23% of all patients. The GI subset showed a median PFS of 11.0 months for everolimus and 3.9 months for placebo. SSA as a previous treatment was associated with 50% of patients. Adverse events for everolimus included stomatitis, infections, diarrhea, and fatigue in descending order of frequency. Considering the result, everolimus may be considered a first-choice treatment for F/H GI-NET. In contrast, SSA shows few adverse events and its treatment continuation may be safer than using everolimus. For a non-midgut patient cohort, everolimus induced an increasing median PFS, similar to its effect on a midgut cohort. Comparing the median PFS of the placebo in midgut and non-midgut patient populations, the non-midgut population showed a poor prognosis. In contrast, everolimus showed the same effect without regard to the origin of the GI-NET. Thus, the selection of treatment, including surgery, chemotherapy and TACE/TAE, may depend on the disease status of each patient.

In conclusion, our study demonstrated the efficacy of SSA in patients with unresectable F/H-NET. Currently, JNETS promotes a NET patient registry (PROP-UP study, UMIN000016380), which is the type of data repository our data requires to be validated. For the development of effective treatments for F/H-NET, collaboration among Asian countries that have relatively large numbers of F/H-NET cases and the creation of an Asian database are warranted.

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Compliance with Ethical Standards

Conflict of interest

All authors do not have potential conflicts of interest to disclose.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This retrospective study was approved by the Institutional Review Board of NCCH (2017-229).

Informed consent

For this type of study formal consent is not required.

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Table 1 Baseline patient characteristics (n=12)

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Age (median, years)	69	Tumor grade		SSA	
		Grade 1	3	Octoreotide	8
		Grade 2	9	Lanreotide (domestic phase Ⅱ trial)	4
Sex		Chromogranin A		Line in SSA	
Man	4	Positive	9	1 line	10
Woman	8	Negative	3	2 line	2
Original site		Ki 67 index		Pre-treatment	
Rectum	10	<2%	3	EMR	1
Stomach	1	2–20%	9	Surgery	8
Duodenum	1			Chemotherapy	2
				RFA	2
Status at start of treatment		Hepatic tumor load		Post-treatment	
Stage Ⅳ	4	≤25%	9	(overlapping)	
Postoperative recurrence	8	>25%	3	TACE/TAE	5
				Everolimus	2
				Lanreotide (domestic phase Ⅱ trial)	1
				Chemotherapy[a] (including clinical trials)	7
Metastasis organ (overlapping)		SRS (Octoreoscan)			
		Positive	2		
Liver	12	Not complied with	10		
Bone	4				
Lung	1				
Pancreas	1				
Functional NET (Carcinoid syndrome)	1				

Abbreviations: TACE/TAE, transcatheter arterial chemoembolization/transcatheter arterial embolization; XELOX, capecitabine/oxaliplatin; S-1, tegafur/gimeracil/oteracil; STZ, streptozotocin; SSA, somatostatin analog; EMR, endoscopic mucosal resection; RFA, radiofrequency ablation; SRS, somatostatin receptor scintigraphy; NET, neuroendocrine tumor

[a]Chemotherapy including XELOX, S-1+STZ, STZ, investigational drugs including mTOR and tyrosine kinase inhibitors

Table 2 Adverse events suspected with use of somatostatin analogs (n=12)

Adverse event	All grades N (%)	Grade 1 N (%)	Grade 2 N (%)
Constipation	6 (50%)	3 (25.0)	3 (25.0)
Fatigue	3 (25.0)	3 (25.0)	0 (0)
Diarrhea	2 (16.7)	2 (16.7)	0 (0)
Abdominal pain	2 (16.7)	2 (16.7)	0 (0)
Injection site reaction	2 (16.7)	2 (16.7)	0 (0)
Decrease in platelets	1 (8.3)	1 (8.3)	0 (0)
Pale stools	1 (8.3)	1 (8.3)	0 (0)

Fig. 1 Kaplan–Meier analysis of (a) progression-free and (b) overall survival (n = 12)

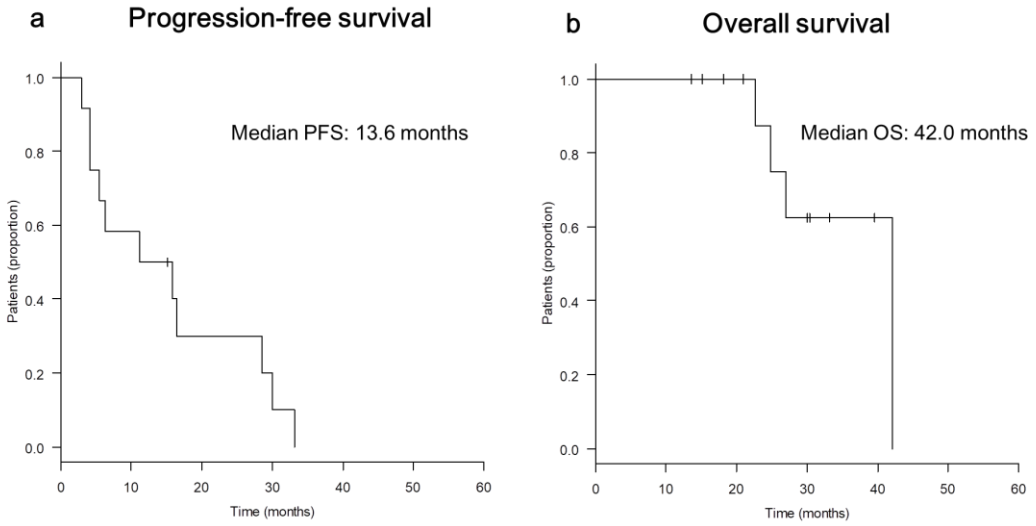
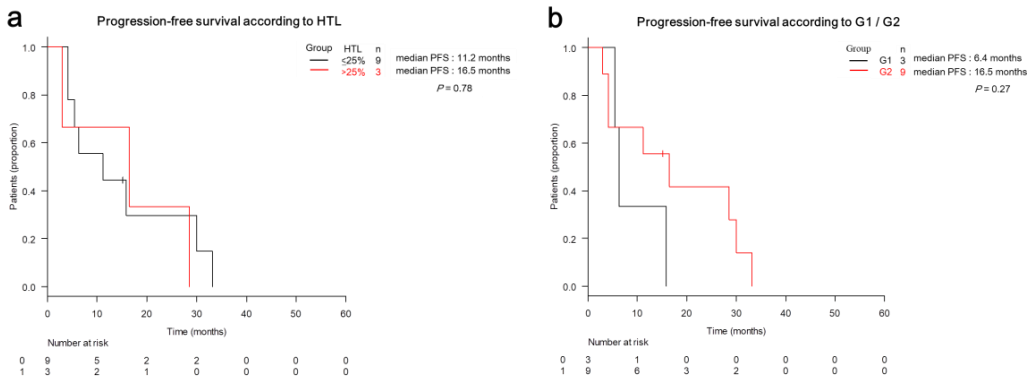
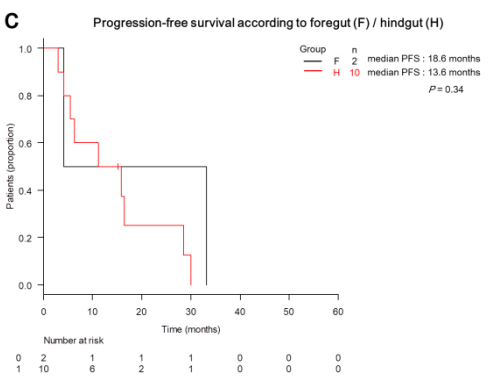
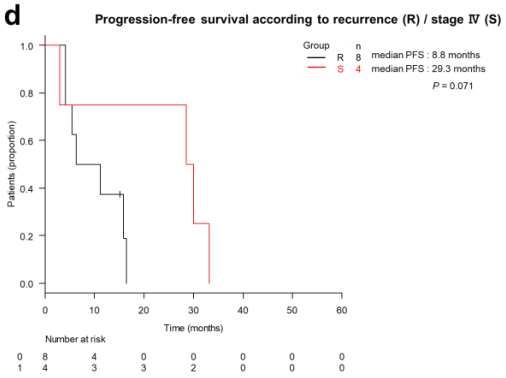


Fig. 2 Kaplan–Meier analysis of progression-free survival compared with (a) hepatic tumor load (HTL; ≤25%, >25%), (b) G1/G2 tumors, (c) foregut/hindgut, (d) disease status (recurrence vs. initial metastatic disease [stage Ⅳ]), and (e) number of organs with metastases other than liver (0 or ≥1).




c
Progression-free survival according to foregut (F) / hindgut (H)
Group n
F 2 median PFS : 18.6 months
H 10 median PFS : 13.6 months
P = 0.34
Patients (proportion)
Time (months)
Number at risk


d
Progression-free survival according to recurrence (R) / stage Ⅳ (S)
Group n
R 8 median PFS : 8.8 months
S 4 median PFS : 29.3 months
P = 0.071
Patients (proportion)
Time (months)
Number at risk

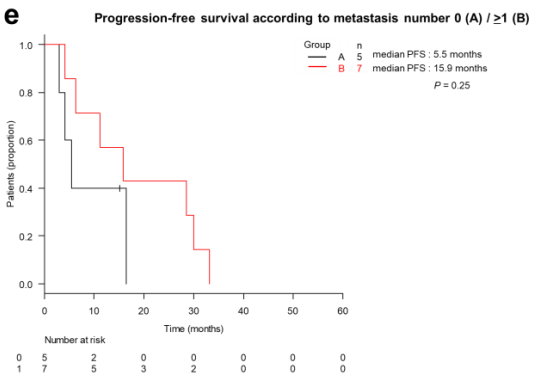

e
Progression-free survival according to metastasis number 0 (A) / ≥1 (B)
Group n
A 5 median PFS : 5.5 months
B 7 median PFS : 15.9 months
P = 0.25
Patients (proportion)
Time (months)
Number at risk

Fig. 3 The best overall response

The greatest change from baseline in the sum of diameters of target lesions.