

Case Report

A Case of Streptozocin Monotherapy for Unresectable Duodenal Neuroendocrine Tumor G2

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Keywords

Neuroendocrine tumor · Duodenal tumor · Streptozocin

Abstract

Background: Duodenal neuroendocrine tumors (NET) are rare, and few reports have demonstrated the effectiveness of chemotherapy for duodenal NET, with not many other treatment options available. Here, we present a case of unresectable duodenal NET G2 that was effectively treated with streptozocin (STZ) monotherapy. We also perform a literature review. **Case Summary:** A 57-year-old man presented with multiple lymph node metastasis, liver metastasis, and bone metastasis that occurred after the primary resection of the duodenal NET G2. His long-term survival was obtained; the duration of stable disease exceeded 1 year and 6 months following STZ monotherapy. In addition, his CA 19–9 levels, which previously were increasing, normalized following treatment. **Conclusion:** To our knowledge, no study has reported the effectiveness of STZ monotherapy for duodenal NET. Our findings demonstrate that for unresectable duodenal NETs, STZ should be first administered as a high volume/single dose to stabilize the disease. However, if the disease progresses, a combination therapy may be effective in obtaining a long-term prognosis of the patient. Furthermore, CA19–9 levels may be an effective factor for determining the therapeutic effect of STZ in NET with other metastases.

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Introduction

Neuroendocrine tumor (NET) is a rare disease [1], originally considered to progress slowly with a low grade. However, in recent years, studies have reported the increased occurrence of NET in the US, Europe, and Japan [1–4].

The first choice of treatment for NETs is surgical resection; however, studies have reported that 40–95% of patients have distant metastases when NET is detected [2].

For this reason, multidisciplinary treatments, including anti-tumor agents, are often required. In Europe and the US, streptozocin (STZ) chemotherapy has been the key treatment for NET for >30 years, and its concomitant use with 5-fluorouracil (FU) and doxorubicin (DOX) is the current standard treatment choice. However, the treatment response rate of duodenal NET is lower than that of pancreatic NET, and the number of reports on duodenal NET in Japan is low [5–14]. In Japan, STZ was approved in 2015. As in our case, STZ is used as a single agent for treating duodenal NET, although cases with its significant effect have rarely been reported in Japan and other countries [4, 6].

Octreoscan has been used for detecting the metastasis and recurrence of NET. However, in Japan, hospitals wherein indium-111-labeled pentetreotide can be performed are limited, and frequently performing Octreoscan is not possible at our hospital. Furthermore, the measurement of chromogranin A has not been approved in Japan. Here, we report about a case of unresectable duodenal NET G2 that was effectively treated with STZ monotherapy and also perform a literature review.

Case Report

A 57-year-old man underwent pancreatoduodenectomy for duodenal bulb NET (G2) (T1 N1 M0 Stage IIIb) in December 2015 (Fig. 1). However, multiple liver metastasis was observed 6 months after the surgery. Therefore, TACE (lipiodol) was performed, which was ineffective, leading to disease progression. Next, everolimus was administered; however, CA 19–9 levels elevated after 6 months of administration, and multiple liver, lymph node, and bone metastasis was confirmed by an octreotide scan. The disease was judged to PD (Fig. 2a). In May 2017, STZ monotherapy (1,000 mg/m²; weekly administrations) was initiated. The CA 19–9 levels decreased after the third course and normalized after the fifth course. One year later, an octreotide scan showed a stable disease (Fig. 2b). However, 1 year later, because CA 19–9 levels increased, the STZ dose was increased to 1,500 mg/m², after which the levels normalized again for the second time (Fig. 3). The STZ dose could be increased to 1,500 mg/m² because the patient could tolerate the increased dose. The progression-free survival of the patient exceeds 1 year and 6 months, with STZ monotherapy ongoing for the patient (56 courses administered).

Patient consent was obtained, and the study was approved by the ethics committee of our hospital.

Discussion

The 5-year survival rate of patients with gastrointestinal NET with liver metastasis is 56–83%, and appropriate control of liver metastatic lesions may lead to better and longer prognosis [8]. Currently, NET is treated with STZ chemotherapy. The response of pancreatic NET to STZ via GLLUT 2 of the pancreatic islets of Langerhans is considered to be the mechanism of action of STZ [15]. Because GLUT 2 is distributed in the small intestine, STZ is expected to be effective for gastrointestinal tract NETs [16]. However, a meta-analysis revealed that the response rate of gastrointestinal tract NET was lower than that of pancreatic NET (odds ratio 0.35; 95% confidence interval 0.18–0.66) [17].

Our case had two main findings. The first finding was that the administration of STZ alone had no severe side effects, and long-term administration is recommended only when effects are observed. A previous study compared the side effects observed in the STZ monotherapy group and the combination group. Nausea and vomiting were observed in 80% of cases in both groups. Regarding myelosuppression, the incidence of leukopenia and thrombocytopenia was 5% in the monotherapy group, that of leukopenia was 73% in the combination group, and that of thrombocytopenia was 27% in the combination group [18].

In our case, nausea and myelosuppression were not observed. Although he complained about awakening in the night after the tenth course, the complaint spontaneously resolved with no treatment required. STZ has been continuously administered for more than a year. Moreover, the patient could continue treatment and have an active social and work life.

A PubMed search for “NET” and “STZ” revealed 10 cases. Among them, two cases reported STZ monotherapy administration [4, 11] (Table 1).

In Oberg et al.’s report [6], the response rate was 14% and OS was 7.5 months, which was short. In contrast, Aoki et al. [4] reported that a long-term SD condition was maintained for patients receiving high STZ dose therapy, such as weekly administrations.

In our case, the disease may have plateaued following the long-term high-dose STZ administration. However, if the patient’s condition deteriorated in the future, we plan to switch to a combination therapy.

The second finding was that STZ decreased CA 19–9 levels. In our case, CA 19–9 levels normalized twice: once, in the early stage of administration and second, after one year. A previous report [6] revealed that 5-hydroxyindoleacetic acid levels decreased following STZ administration, but CA 19–9 levels did not.

CA 19–9 levels alone may not reflect the disease state, and the mechanism underlying the decrease in CA 19–9 levels remains unknown, although STZ may have resulted in decreasing CA 19–9 levels. An octreotide scan is a method specific for NET. In this method, indium 111-labeled pentetreotide is intravenously injected, and a scan is performed twice, after 4 and 24 h. It was included in the national insurance indication in Japan in 2015. In Japan, there are limited hospitals that perform indium-111-labeled pentetreotide imaging, and our hospital is not one of them. Performing octreotide scans frequently in daily practice is not practical. In addition, a chromometric A measurement is not insurance certified. CA 19–9 level measurement and contrast-enhanced CT can be performed in most hospitals and thus are better to conduct on a daily basis compared with Octreoscan, which should be performed only when an abnormality is observed.

In conclusion, for unresectable duodenal NET, such as in our case, first, STZ should be administered as a high volume/single dose, with the aim to stabilize the disease state. However, if the disease progresses, switching to a combination therapy may be effective in obtaining long-term prognosis of the patient. In addition, CA19–9 levels may be an effective method of determining the therapeutic effect of STZ in NET with other metastases.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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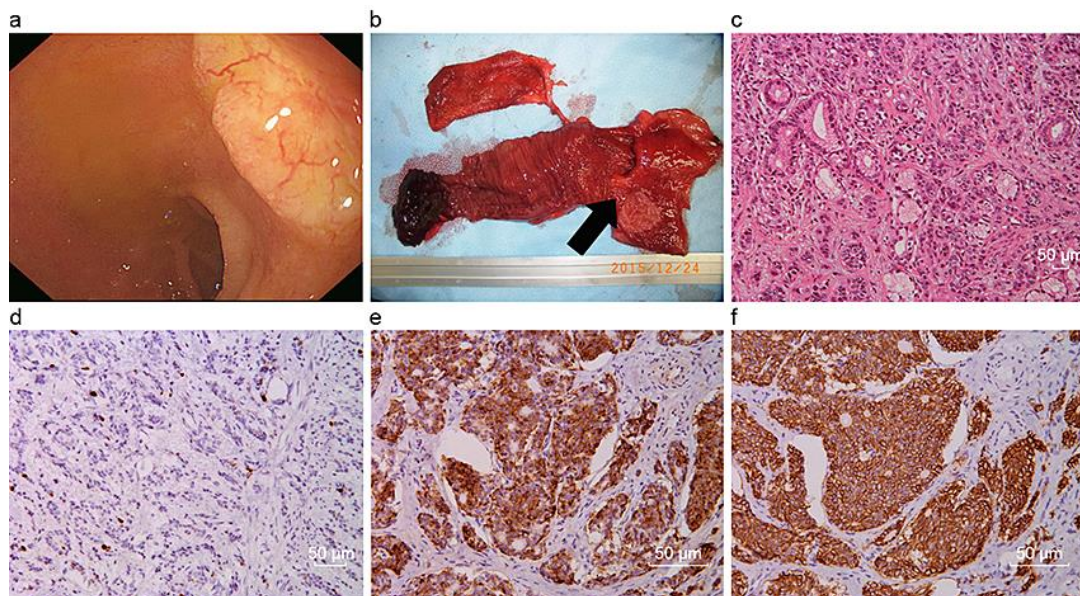


Fig. 1. **a**, Upper endoscopic examination: the tumor size was 8 mm on the duodenal bulb. **b**, Pancreaticoduodenectomy was performed: the black arrow indicates the tumor. **c**, The tumor comprises small-sized cells with granular eosinophilic cytoplasm, central round nuclei, coarse-clustered chromatin and inconspicuous nuclei (hematoxylin and eosin stain, $\times 200$). Immunohistochemical staining. The tumor cells show a Ki-67 index of approximately 5% (**d**) with positive expressions for chromogranin A (**e**) and synaptophysin (**f**).

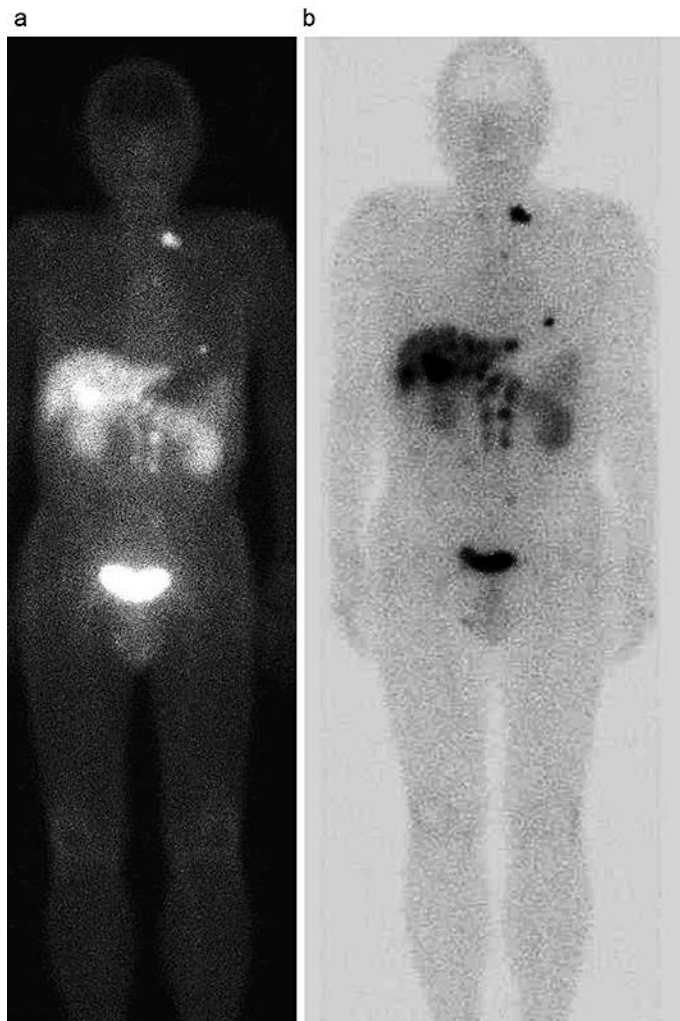


Fig. 2. Octreoscan: comparison 1 year after administration of streptozocin monotherapy before (**a**) and after 42 courses (**b**).

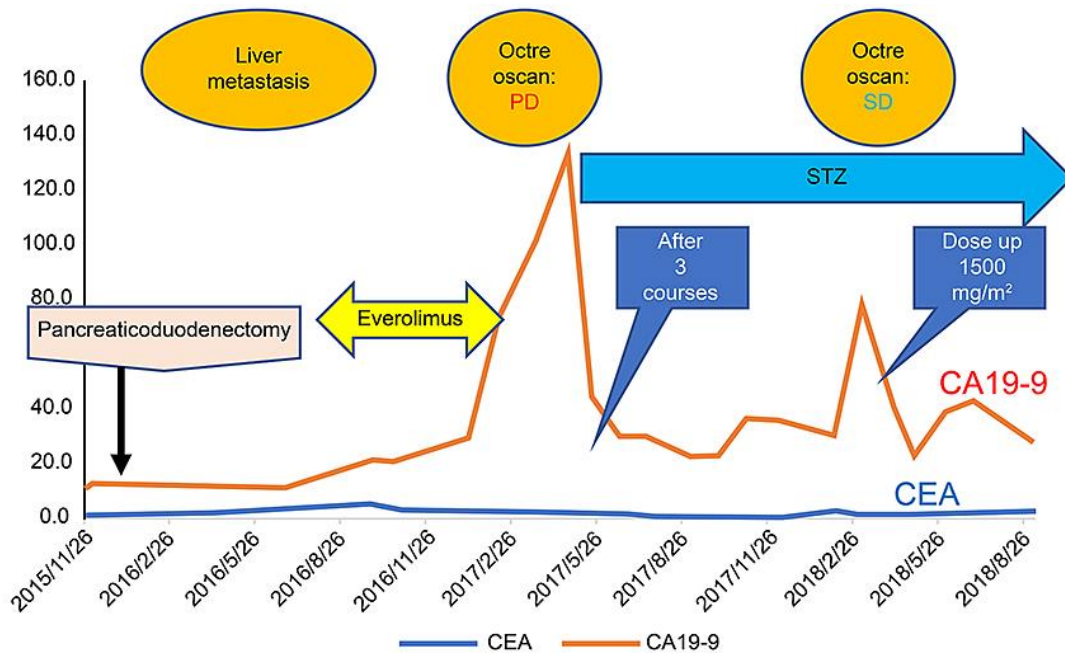


Fig. 3. Treatment course.

Table 1. Report on the administration of streptozocin to the gastrointestinal tract NET

Author year	Year	n	Regimen	ORR (%)	PFS (m)	OS (m)
Moertel [5]	1979	47	STZ* ¹ + CPA 1,000 mg/m ²	24 (10/42)	-	12.5
		42	STZ* ¹ + 5-FU 400 mg/m ² /day	21 (8/38)		11.2
Engstrom [9]	1984	104	STZ* ¹ + 5-FU 400 mg/m ² /day		7.8 (31 w)	16.0 (64 w)
		91	DOX 60 mg/m ²		6.5 (26 w)	12.0 (48 w)
Bukowski [10]	1987	65	History of heart disease (+)		-	7.6
			STZ 400 or 600 mg/m ² day 1, day 8			
Oberberg [6]	1987	7	History of heart disease (-)			12.9
			STZ 200 or 400 mg/m ² day 1, day 8			
Oberberg [15]	1989	7	STZ* ¹	14 (1/7)	-	7.5
		24	STZ* ¹ + 5-FU 400 mg/m ² /day	8 (2/24)		18
Sun [12]	2005	10	STZ* ¹ + 5-FU 400 mg/m ² /day	0 (0/10)	-	-
		10	IFN	50 (5/10)		
Dahan [13]	2009	78	STZ* ¹ + 5-FU 400 mg/m ² /day	15 (12/78)	5.3	24.3
		85	DOX 40 mg/m ² + 5-FU 400 mg/m ² /day	13 (11/85)	4.5	15.7
Turner [7]	2010	32	STZ* ¹ + 5-FU 400 mg/m ² /day	3 (1/32)	5.5	30.4
		32	IFN	9 (3/32)	14.1	44.3
Aoki [4]	2011	9	STZ 1,000 mg/m ² /day + 5-FU 500 mg/m ² /day + CDDP	22 (2/9)	-	-
Meyer [14]	2014	4	Daily* ³ or Weekly* ⁴ (STZ mono)	25 (1/4)	-	-
		4	Daily* ³ or Weekly* ⁴ (UFT,5FU combination)	25 (1/4)	-	-
Meyer [14]	2014	9	STZ* ¹ + CAP	6 (1/17)	-	-
		8	STZ* ¹ + CAP + CDDP			

STZ, streptozocin; 5-FU, fluorouracil; DOX, doxorubicin; CPA, cyclophosphamide; CAP, capecitabine; CDDP, cisplatin; IFN, interferon- α . *¹: Daily, 500 mg/m²/day (1 course for 6 weeks, except for the studies of Engstrom et al. [9] and Sun et al. [12], in which 1 course was administered for 10 weeks. *²: 1 course 3 weeks, maximum 6 cycle. *³: Day 1–5. *⁴: 1,000 mg/body/week, or 1,000 mg/body/2 weeks.