A case of advanced pancreatic neuroendocrine tumor in which octreotide long-acting repeatable was effective after failure of everolimus and sunitinib

Hironori Kitade¹ · Koushiro Ohtsubo⁴ · Kengo Hokkoku¹ · Mitsue Mori¹ · Robert Yoshiyuki Osamura⁵ · Hiroshi Sakuma² · Masuo Nakai² · Seiji Yano^{3,4}

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Abstract

Molecular targeted drugs, such as everolimus and sunitinib, have shown efficacy against advanced pancreatic neuroendocrine tumors. Octreotide, a somatostatin analogue, improves the hormone-related symptoms in patients with neuroendocrine tumors. Furthermore, it has been reported that octreotide has antitumor activity in patients with metastatic midgut neuroendocrine tumors. However, whether octreotide has anti-proliferative effects in patients with advanced pancreatic neuroendocrine tumors is not fully understood. We report a 71-year-old man with multiple liver metastases of pancreatic neuroendocrine tumor. He was treated with everolimus 10 mg daily and sunitinib 25 mg daily on days 1–14 every 3 weeks at the physician's discretion. However, these molecular targeted drugs were discontinued due to disease progression or severe adverse effects. Octreotide long-acting repeatable was administered continuously from the initiation of everolimus treatment. The tumor marker level markedly decreased and the metastatic liver lesions showed shrinkage with octreotide treatment. Immunohistochemistry of tumor specimens obtained before treatment showed that somatostatin receptor 2, a high-affinity receptor for octreotide, was highly expressed. The clinical course of this patient suggested that octreotide long-acting repeatable may be a treatment option for advanced pancreatic neuroendocrine tumors after failure of everolimus and sunitinib. Further clinical trials are warranted to determine whether the expression of somatostatin receptor 2 in tumor tissues is predictive of octreotide efficacy.

Keywords Pancreatic neuroendocrine tumor · Octreotide · Somatostatin receptor

Introduction

Pancreatic neuroendocrine tumors (PNETs) are relatively uncommon malignancies arising from endocrine cells of the pancreas [1]. The median survival of patients with advanced lesions is about 2 years [2]. Surgery is the main treatment for early-stage disease [3]. Pharmacological treatments, such as somatostatin analogues (SSAs) and molecular targeted drugs, are administered in patients with advanced PNETs [4–7].

Octreotide, which is the first developed SSA, improves the hormone-related symptoms associated with neuroendocrine tumors (NETs). Furthermore, it has been shown that octreotide long-acting repeatable (LAR) has antitumor effects in patients with midgut NETs [8]. However, there is little evidence that octreotide has antitumor effects in PNETs. Here, we report a case of advanced PNET in which

✉ Hironori Kitade
hiro.kitacchi@gmail.com

¹ Department of Pharmacy, Houju Memorial Hospital, 11-71, Midorigaoka, Nomi, Ishikawa 923-1226, Japan

² Department of Surgery, Houju Memorial Hospital, 11-71, Midorigaoka, Nomi, Ishikawa 923-1226, Japan

³ Outpatient Cancer Chemotherapy Center, Houju Memorial Hospital, 11-71, Midorigaoka, Nomi, Ishikawa 923-1226, Japan

⁴ Division of Medical Oncology, Cancer Research Institute, Kanazawa University, 13-1 Takara-machi, Kanazawa, Ishikawa 920-0934, Japan

⁵ Department of Pathology, International University of Health and Welfare Mita Hospital, 1-4-3 Mita, Minato-ku, Tokyo 108-8239, Japan

octreotide LAR had an antitumor effect after failure of sunitinib and everolimus treatment.

Immunohistochemical (IHC) staining for somatostatin receptor (SSTR) 2

Formalin-fixed and paraffin-embedded section from our case was analyzed. IHC staining was performed by the DAKO Envision kit (DAKO) using rabbit monoclonal anti-SSTR2 antibody (1:100, catalog number #3582-1, Epitomics, USA).

Case presentation

We present a 71-year-old man who was diagnosed with stage IV PNET with multiple liver metastases. He had a history of hypertension and had taken amlodipine 5 mg daily. He consumed alcohol and had a history of smoking a pack of cigarettes daily for about 45 years. Laboratory findings showed the following results: alanine transaminase 65 U/L (normal range 4–44 U/L), aspartate transaminase 75 U/L (8–38 U/L), serum amylase 170 U/L (41–112 U/L), neuron-specific enolase (NSE) 19.7 ng/mL (< 16.3 ng/mL), and progastrin-releasing peptide 35.4 pg/mL (< 81 pg/mL). Computed tomography (CT) scan showed a pancreatic head mass 36 mm in diameter with multiple liver metastases. A needle biopsy of the liver metastasis showed multiple neoplastic cells with small round nuclei arranged in sheets, and rosette-like structures on hematoxylin and eosin staining (Fig. 1a). The tumor was positive for chromogranin, synaptophysin, and CD56, and the MIB-1 labeling index was 1–2%. This case was diagnosed as PNET (G1) according to the World Health Organization 2010 classification [9].

Everolimus 10 mg daily was administered as the first-line treatment in May 2012 (Fig. 2a, b). One month later, the

patient developed flushing of the facial skin. Although there was a possibility that this symptom was the anaphylaxis caused by everolimus, we thought that the flushing of the facial skin may have been a symptom of carcinoid syndrome. Then octreotide LAR 20 mg monthly was added to everolimus monotherapy in July 2012. His flushing of the facial skin was improved after administration of octreotide, but his circulating NSE level, which could be an effective surrogate marker of treatment of PNETs, was elevated and CT showed progression of the liver metastases 4 months after the start of everolimus treatment (Fig. 2a, c). Furthermore, he was diagnosed with disseminated intravascular coagulation (DIC), as he had bleeding under the skin and laboratory findings showed platelet count of 65,000/ μ L, fibrin degradation products 68.6 μ g/mL (0–10 μ g/mL), D-dimer 34.2 μ g/mL (< 1.0 μ g/mL) and fibrinogen 130 mg/dL (150–400 mg/dL) at this time, indicating that DIC score was 7 points. He began the treatment with subcutaneous injection of heparin calcium 10,000 units per day and then platelet count was increased around 100,000/ μ L in September 2012.

As it was concerned that severe thrombocytopenia will be developed after treatment with standard dose sunitinib for PNETs, low-dose sunitinib 25 mg daily on days 1–14 every 3 weeks was initiated in September 2012 at the physician's discretion, while octreotide LAR was administered continuously. However, the patient developed grade 2 hypertension, grade 3 neutropenia, and grade 2 thrombocytopenia after 2 months of sunitinib treatment. Furthermore, his NSE levels further increased, and CT indicated that the hepatic metastases had progressed (Fig. 2a, d). He discontinued sunitinib therapy and continued octreotide LAR monotherapy.

Interestingly, the NSE levels markedly decreased and the metastatic liver lesions showed shrinkage by CT 6 months after administration of octreotide LAR (Fig. 2a, e). As we believed that octreotide LAR treatment had an antitumor effect on the liver metastases, the dose was increased to

Fig. 1 **a** Hematoxylin–eosin staining of the tumor tissue section ($\times 400$). **b** Immunohistochemical analysis of somatostatin receptor 2 ($\times 400$)

Fig. 2 **a** Serum NSE levels and the timing of the each CT scan during treatment. **b** Before treatment with everolimus in May 2012. Multiple liver metastases were visible. **c** Four months after administration of everolimus. Liver metastases were progressed. **d** Two months after administration of sunitinib. Hepatic metastases had further progressed.

e Six months after addition of octreotide LAR. Multiple metastatic liver lesions showed shrinkage. **f** Prior to death. Ascites increased and hepatic enlargement was found. *CT* computed tomography, *LAR* long-acting repeatable, *NSE* neuron-specific enolase

30 mg monthly at the physician's discretion. He continued treatment, with disease stabilization by CT after 6 months. However, CT after 6 months showed progression of the metastatic liver lesions and increased ascites. Because other effective agents, such as lanreotide and streptozotocin, were not approved in Japan at the time, he received the best supportive care. Thereafter, he developed abdominal fullness, decreased appetite, and severe fatigue, and died in April 2014 (Fig. 2f).

We investigated the IHC expression of SSTR2 in the tumor before octreotide LAR administration. SSTR2 is mainly expressed in PNETs and binds octreotide with high affinity [10]. IHC analysis showed that SSTR2 was strongly expressed in the tumor tissue section (Score 3, Fig. 1b).

This case report was approved by the ethics review committee of the Houju Memorial Hospital (Ishikawa, Japan) (No. 16-6).

Discussion

We report a patient with metastatic PNET in whom octreotide LAR showed antitumor efficacy after failure of molecular targeted drug therapy. Somatostatin inhibits the secretion or synthesis of peptide hormones in various neuroendocrine cells. Five SSTR subtypes (SSTR1-5) have been identified, and SSTRs are expressed in most PNETs [11]. Subtypes SSTR2 and 5 play a central role in inhibiting hormone secretion [12]. Subtypes SSTR1, 2, 4, and 5 are important in regulating cell proliferation, and SSTR2 and 3 play a role in inducing cell apoptosis [13]. It is well known that octreotide binds preferentially to SSTR2 and 5, although it has moderate affinity for SSTR3 [14]. Of these, SSTR2 has the greatest affinity for octreotide. In this case, octreotide LAR was administered concurrently with everolimus or sunitinib treatment, but molecular targeted drugs were discontinued

because of disease progression or severe adverse effects. In this clinical course, decrease in NSE levels and tumor shrinkage was observed after discontinuation of sunitinib. There is a possibility that sunitinib has also an antitumor effect. Indeed, it has been reported that low-dose sunitinib is effective in patients with advanced PNETs [15]. However, the relative dose intensity and exposure period of sunitinib in our case are very low as compared to the previous report. In addition, the tumor lesions showed disease stabilization after octreotide monotherapy. Ricci et al. reported that tumor shrinkage was observed after 6 months of octreotide LAR therapy and was lasting after 10 months of treatment in an endocrine pancreatic tumor [16]. Therefore, although there were no reports concerning the mechanism of delayed response by the treatment of octreotide, we strongly suggest that octreotide LAR had antitumor efficacy after failure of everolimus or sunitinib treatment.

We speculate that the mechanism of octreotide LAR efficacy is associated with the strong expression of SSTR2 in tumor tissues, leading to tumor cell growth inhibition and induction of apoptosis. However, previous studies have shown that there is no correlation between SSTR2 expression and octreotide effectiveness [17]. Other studies have reported that SSTR2 expression is an independent prognostic marker in NETs [18]. Therefore, further investigation on the molecular level is needed to elucidate why octreotide shows antitumor effects in some patients with PNETs and the relationship between SSA effectiveness and the expression level of SSTR2.

There is no consensus as to whether octreotide actually has antitumor efficacy for PNETs, although there are several reports in which it shows efficacy [19]. Panzuto et al. reported that pancreatic tumors or distant extrahepatic metastases are predictors of poor efficacy of SSAs, and patients achieving response after 6 months of treatment maintain it throughout a long-term administration [20]. Although our case did have multiple liver metastases, which is considered a factor of poor efficacy of octreotide treatment in PNETs, it is very interesting that octreotide LAR showed antitumor efficacy and the patient continued treatment for 1.5 years.

A previous study reported that lanreotide, a second SSA with improved affinity for SSTR2, showed anti-proliferative effects in SSTR-positive NETs [4]. Moreover, Wolin et al. reported that pasireotide LAR, which is a multireceptor ligand analogue that has high affinity for SSTR1, 2, 3, and 5, showed a trend toward higher tumor control than octreotide LAR [5]. Recent studies have reported that radiolabeled SSA therapy with 90-Yttrium-DOTATOC or 177-Lutetium-DOTATE has shown effectiveness for midgut NETs [21, 22]. Therefore, SSAs should be considered not only for controlling hormonal secretion but also for disease stabilization and tumor shrinkage.

The clinical course of this case suggests that octreotide LAR may be one of the treatment options in advanced PNETs. Further clinical trials are warranted to determine whether the expression of SSTR2 in tumor tissues is predictive of octreotide efficacy.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Human rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Written informed consent was obtained from the patient's next of kin for the publication of this case report and any accompanying images.

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