Long-Term Disease Control of a Pancreatic Neuroendocrine Tumor with Lanreotide Autogel[®]: A Case Report

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Key Words

Pancreatic neuroendocrine tumor · Somatostatin analog · Lanreotide Autogel[®]

Abstract

The CLARINET study (ClinicalTrials.gov: NCT00353496) showed that somatostatin analogs are able to stabilize tumor growth in patients with intestinal and pancreatic neuroendocrine tumors (NETs). Here, we present a case of NET originating from the pancreatic tail that was treated with lanreotide Autogel[®]. A 60-year-old patient underwent resection of a pancreatic NET with splenectomy and distal pancreatectomy. Four months after surgery, there was an increase in chromogranin A levels, along with a hypercaptating lesion of approximately 3.5 cm at the residual part of the pancreatic corpus. Treatment with 30 mg monthly-administered octreotide long-acting release (LAR) was initiated. After 3 months of treatment, a control CT scan revealed diffuse metastases in the liver, although the patient presented no symptoms and liver tests were normal. Due to difficulties with the administration of octreotide LAR, treatment was switched to lanreotide Autogel[®] 120 mg, administered as monthly deep-subcutaneous injections. Progression-free survival, as shown by 3-monthly CT scans, was obtained for 2 years without the need to increase the lanreotide Autogel[®] dose, and the patient reported no side effects. After these 2 years, deterioration of the patient's clinical status and weight loss were observed, along with increased size of the liver lesions and appearance of peritoneal metastases. Chemotherapy treatment with cisplatin-epirubicin was initiated, while the lanreotide Autogel[®] injections were continued. After three chemotherapy cycles, a rapid decline in the patient's quality of life was noted, and she requested discontinuation of the chemotherapy and lanreotide injections. One month later, the patient died due to clinical progressive disease.

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Introduction

Neuroendocrine tumors (NETs) are relatively rare tumors originating from diffuse endocrine cells throughout the body. Pancreatic NETs occur in approximately 1 person per 100,000 and account for 1–2% of all pancreatic neoplasms [1]. The majority of pancreatic NETs are hormonally silent.

Somatostatin analogs provide good symptom control in patients with hormone-secreting NETs but also stabilize tumor growth, as described in several reports (overviews in [2] and [3]). In clinical practice, two somatostatin analogs are currently available as long-acting release (LAR) formulations administered once a month: octreotide and lanreotide. In a randomized, double-blind study (PROMID), conducted in a mixed functioning and non-functioning gastroentero-NET population (n = 85), octreotide LAR significantly increased the time to tumor progression compared to placebo in well-differentiated intestinal NETs (Ki67 <2%) with limited hepatic invasion (<10%) [4]. In a recently completed randomized, double-blind trial (CLARINET), patients treated with lanreotide Autogel® had significantly longer progression-free survival compared with placebo for well- to moderately-differentiated intestinal and pancreatic NETs (Ki67: <10%), even with significant liver invasion (>25%) [5].

Here, we report the use of lanreotide Autogel® in a patient with pancreatic NET and diffuse liver metastases. The treatment, administered once a month, stabilized disease progression for 2 years.

Case Report

In March 2011, a 60-year-old woman presented at the gastroenterology unit of our hospital (AZ Nikolaas, Sint-Niklaas) with gastrointestinal bleeding (table 1). Her medical history reported a deep venous thrombosis with lung embolism in 1999, gallbladder lithiasis, uterus myomatosus and a psychiatric disorder (anxiety and depression). Gastroscopy revealed esophageal varices that were successfully ligated. In addition, a CT scan of the abdomen showed a large tumor (diameter approximately 10 cm) in the left hypochondriac region, located cranial to the tail of the pancreas and expanding into the spleen area (fig. 1a–d). The tumor contained multiple calcifications in the spleen area and around the fundus of the stomach. A pancreatic tail tumor extending into the spleen or a primary splenic tumor was suspected. There was no invasion of the kidneys or adrenal glands, no retroperitoneal adenopathy, no parenchymal metastasis in the liver and no bone lesions. A diagnostic laparoscopy was performed. Anatomopathological examination of limited biopsy material showed the presence of a tumor with morphological and immunohistochemical features suggesting metastasis or extension of a clear cell renal cell carcinoma in the pancreas, although the possibility of an adrenocortical carcinoma could not be excluded. Hematoxylin and eosin staining revealed a lesion with a solid and nested growth pattern containing cells with clear cytoplasm, well-defined cell borders and small, slightly pleomorphic nuclei (fig. 2a, b). The tumor showed a strong positive reaction to staining for vimentin (fig. 2d) and focal positivity for CD10 (fig. 2c). It also showed strong staining with pancytokeratin (CK AE1/AE3) and focal positivity for synaptophysin; there was no immunoreactivity for CD45 (LCA).

Due to the widespread nature of the tumor in the upper abdomen and the inconclusive anatomopathological examination, the patient underwent surgery in a university center (UZ Leuven). In June 2011, the tumor was resected with splenectomy and distal pancreatectomy.

The anatomopathological examination was compatible with a NET originating from the pancreatic tail, which could have arisen from an intrasplenic pancreatic remnant. Microscopically, the tumor was strongly vascularized, with a heterogeneous population of tumor cells and varying atypical nuclei. Immunohistochemical analysis showed diffuse membrane expression of prekeratin and inhibin, partial expression of epithelial membrane antigen, a focal, dot-like expression of CK7, a weak partial expression of synaptophysin and a strong diffuse expression of CK20. A focal expression of MelanA was also observed, while neurofilament and calretinin were not expressed. The tumor had invaded the spleen and peripancreatic fat, which was resected in toto. The tumor was diagnosed as a stage II pancreatic NET, with a Ki67 index of 10%. Since the PET/CT scan in the initial staging showed no metastases, no treatment was initiated but a close clinical, biochemical and radiological follow-up was planned.

In October 2011, an increase in the level of the tumor marker chromogranin A was noted during follow-up laboratory testing. A CT scan of the abdomen revealed a hypercapitating lesion of approximately 3.5 cm, located at the residual part of the pancreatic corpus, without enlargement of the pancreas. Due to its hypervascular character, a residual tumor or tumor relapse was suspected. Because of this early relapse after extensive surgical resection, we initiated treatment with a LAR formulation of octreotide (Sandostatin LAR® 30 mg, Novartis), administered intramuscularly once a month. Extensive analysis of CT scan images after 3 months of treatment was planned.

The control CT scan in January 2012 revealed multiple small lesions with early arterial enhancement in the parenchyma of the liver, indicative of hypervascular metastases (fig. 3a–c). However, the patient presented no symptoms and biochemical tests showed normal liver function. Due to difficulties with the administration of the Sandostatin LAR® injections (the nurses reported difficulties with handling the syringes and with making a homogeneous solution), the treatment was switched to lanreotide Autogel® 120 mg (Somatuline® Autogel®, Ipsen NV), administered once a month. This long-acting somatostatin analog is provided as a prefilled syringe and is administered deep-subcutaneously in the upper outer quadrant of the buttocks. No difficulties with the administration of lanreotide Autogel® 120 mg were encountered, and the patient reported no side effects. Follow-up visits with CT scans were performed every 3 months. The disease at the residual pancreas and liver remained stable until November 2013. Chromogranin and neuron-specific enolase levels were also assessed and were found to be normalizing.

Deterioration in the clinical status of the patient and weight loss were noted from November 2013 on. A CT scan revealed an increase in the size of the liver lesions and presence of peritoneal metastases with a low level of ascites (fig. 3d, e). A chemotherapy course consisting of 6 cycles of cisplatin-epidoxifen was initiated in December 2013. This treatment was chosen above newer targeted therapies, such as sunitinib and everolimus, because of the aggressive evolution of the pancreatic NET in our patient. The chemotherapy was administered every 3 weeks according to the following schedule: day 1, cisplatin 80 mg/m²; day 1, 2 and 3, epidoxifen 100 mg/m². The lanreotide Autogel® 120 mg injections were continued during the chemotherapy course. After 3 cycles of chemotherapy, we saw a rapid decline in the quality of life of our patient and she refused any further treatment; the lanreotide injections were also stopped. Palliative care at home was initiated. The patient died due to clinical progressive disease 1 month after the chemotherapy had been stopped.

Discussion

Somatostatin analogs provide good symptom control in patients with a functionally active NET. In addition, they have been shown to have antiproliferative effects *in vitro* [6–9]. Here, we present a case of pancreatic NET which was treated with octreotide LAR for 3 months after resection. Due to difficulties with the administration of octreotide LAR, treatment was switched to lanreotide Autogel® 120 mg, after which progression-free survival was achieved for almost 2 years without the need to intensify the therapy.

Evidence of the inhibitory effect of somatostatin analogs on tumor growth in humans comes mainly from non-randomized open-label studies (overviews in [2] and [3]). PROMID was the first phase III double-blind randomized study to show that octreotide LAR significantly increased the time to tumor progression compared to placebo [4]. The median time to tumor progression was 14.3 months in the octreotide group and 6.0 months in the placebo group (hazard ratio 0.34, 95% confidence interval 0.20–0.59). After 6 months of treatment, stable disease was observed for 66.7% of patients in the treatment group compared to 37.2% of patients in the placebo group [4]. The PROMID study constituted a small clinical trial dataset (85 patients), and results were mainly positive for patients with well-differentiated (Ki67 index <2%) midgut NET with limited liver involvement (<10%) and for whom the primary tumor was resected. In the phase III CLARINET study, in which lanreotide Autogel® 120 mg was administered once every 4 weeks, patients with either well- or moderately-differentiated (Ki67 index <10%) NET of gastrointestinal or pancreatic origin were recruited [5]. Of the 204 enrolled patients, 45% had a primary pancreatic NET and constituted a subgroup that was not included in the PROMID study. Treatment with lanreotide led to significantly longer progression-free survival compared to placebo (hazard ratio 0.47, 95% confidence interval 0.30–0.73). At the end of the 2-year treatment, 62% of the lanreotide-treated patients had not progressed, compared to 22% of the placebo-treated patients [5]. Our case report provides findings from a real-life setting that are consistent with the recently published CLARINET results.

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Disclosure Statement

Dr. Lybaert is a consultant for Ipsen NV. Erik Van Hul and Heidi Woestenborghs have no conflicts of interest to declare.

References

- 1 Oberg K, Eriksson B: Endocrine tumours of the pancreas. *Best Pract Res Clin Gastroenterol* 2005;19:753–781.
- 2 Modlin IM, Pavel M, Kidd M, Gustafsson BI: Review article: Somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours. *Aliment Pharmacol Ther* 2010;31:169–188.

- 3 Strosberg J, Kvols L: Antiproliferative effect of somatostatin analogs in gastroenteropancreatic neuroendocrine tumors. *World J Gastroenterol* 2010;16:2963–2970.
- 4 Rinke A, Muller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, Mayer C, Aminossadati B, Pape UF, Blaker M, Harder J, Arnold C, Gress T, Arnold R; PROMID Study Group: Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol* 2009;27:4656–4663.
- 5 Caplin ME, Pavel M, Cwikla JB, Phan AT, Raderer M, Sedlackova E, Cadiot G, Wolin EM, Capdevila J, Wall L, Rindi G, Langley A, Martinez S, Blumberg J, Ruzsniowski P; CLARINET Investigators: Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med* 2014;371:224–233.
- 6 Grozinsky-Glasberg S, Shimon I, Korbonsits M, Grossman AB: Somatostatin analogues in the control of neuroendocrine tumours: efficacy and mechanisms. *Endocr Relat Cancer* 2008;15:701–720.
- 7 Susini C, Buscail L: Rationale for the use of somatostatin analogs as antitumor agents. *Ann Oncol* 2006;17:1733–1742.
- 8 Theodoropoulou M, Zhang J, Laupheimer S, Paez-Pereda M, Erneux C, Florio T, Pagotto U, Stalla GK: Octreotide, a somatostatin analogue, mediates its antiproliferative action in pituitary tumor cells by altering phosphatidylinositol 3-kinase signaling and inducing Zac1 expression. *Cancer Res* 2006;66:1576–1582.
- 9 Florio T: Molecular mechanisms of the antiproliferative activity of somatostatin receptors (SSTRs) in neuroendocrine tumors. *Front Biosci* 2008;13:822–840.

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Table 1. Time line

March 2011	Patient hospitalized with gastrointestinal bleeding due to esophageal varices. CT scan: large tumor in the left hypochondriac region.
June 2011	Resection of the tumor with splenectomy and distal pancreatectomy.
October 2011	Increased levels of tumor marker chromogranin A. CT scan: residual tumor or tumor relapse. Treatment with octreotide LAR 30 mg was started, administered monthly.
January 2012	CT scan: metastases in the liver (patient asymptomatic, liver tests normal). Treatment was switched to lanreotide Autogel® 120 mg.
January 2012– November 2013	Stable disease. CT scan: every 3 months. Lanreotide Autogel® 120 mg: every month.
November 2013	Deterioration in clinical status, weight loss. CT scan: increased size of liver lesions, appearance of peritoneal metastases.
December 2013	Initiation of chemotherapy (cisplatinum-etoposide, every 3 weeks). Continuation of lanreotide Autogel® 120 mg.
February 2014	Rapid decline in quality of life. Discontinuation of chemotherapy and lanreotide Autogel® 120 mg, as per request of the patient.
March 2014	Patient deceased.

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Fig. 1. CT scan at diagnosis (April 2011). The CT scan of the abdomen revealed a large tumor in the left hypochondriac region, located cranial to the tail of the pancreas and expanding into the spleen; there was no invasion of the kidneys or adrenal glands.

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Fig. 2. Microscopic examination of the tumor biopsy. **a, b** Hematoxylin and eosin staining showed a lesion with a solid and nested growth pattern containing cells with clear cytoplasm, well-defined cell borders and small, slightly pleomorphic nuclei. Focal positivity for CD10 (**c**) and strong vimentin immunoreactivity (**d**) was observed.

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January 2012:

November 2013:

Fig. 3. CT scans at follow-up visits. **a–c** The CT scan in January 2012 revealed multiple small lesions with early arterial enhancement in the parenchyma of the liver, indicative of hypervascular metastases. No ascites was observed. **d, e** The CT scan in November 2013 revealed an increase in size of the liver lesions and presence of peritoneal metastases with a low level of ascites.