
Long-Term Management of a Patient with Well-Differentiated Pulmonary Neuroendocrine Carcinoma: A Case Report

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Key Words

Neuroendocrine tumors · Well-differentiated pulmonary neuroendocrine tumors · Pulmonary neuroendocrine tumors · Everolimus · Octreotide long-acting repeatable

Abstract

Pulmonary neuroendocrine tumors (NET) are rare, and very few published reports have described the long-term treatment of patients with this disease. Current treatment options for patients with metastatic well-differentiated pulmonary NET are limited. This case report details the long-term treatment of a 62-year-old female patient with well-differentiated pulmonary NET and multiple liver metastases. The heavily pretreated patient achieved radiographic stability in measurable disease, improvement in nonmeasurable disease, and symptomatic improvement over 3 years while receiving the combination of everolimus and octreotide long-acting repeatable (LAR). Treatment was well tolerated without mucositis, rash, or pneumonitis. This case report suggests that the combination of everolimus and octreotide LAR may be a novel treatment option for heavily pretreated patients with metastatic well-differentiated pulmonary NET, but these findings require further analysis in clinical trials.

Introduction

Neuroendocrine tumors (NET) are composed of mutated cells that contain features of both nerve cells and hormone-producing endocrine cells [1]. The neuroendocrine system is present in most tissues, and these tumors can arise in numerous places, but most commonly they are found in the gastrointestinal and pulmonary systems. The location, functional

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status, and differentiation of the tumor are used to classify and treat the disease [2]. Functional tumors are defined by the nature of hormones or peptides secreted. Nonfunctional tumors are nonsecretory and are defined by their location of origin; they present with symptoms such as pain, obstruction, or bleeding. The pathological classification of NET ranges from well differentiated to poorly differentiated, and clinical behavior corresponds to differentiation, with well-differentiated tumors growing more slowly than others [2, 3]. Liver metastases from NET are common and, outside of local therapy, associated with low response rates to systemic therapies [4].

The pulmonary and gastrointestinal systems are the most common sites of primary NET [1]. Although they vary in behavior, pulmonary NET generally have a better prognosis than other pulmonary carcinomas. The spectrum of pulmonary NET includes low grade or well differentiated [i.e. typical carcinoid (TC)], intermediate grade (i.e. atypical carcinoid), and high grade or poorly differentiated (i.e. large cell neuroendocrine carcinoma and small cell lung carcinoma) [5–7]. Well-differentiated NET are more likely to be functional and may have asthma-like symptoms as well as carcinoid syndrome [8].

Well-differentiated NET (TC and atypical carcinoid) account for up to 2% of pulmonary neuroendocrine carcinomas, with the remainder composed of small cell lung carcinoma, non-small cell lung carcinoma, and large cell neuroendocrine carcinoma [7, 9–11]. Although pulmonary NET are traditionally described as a continuous spectrum of diseases, recent molecular and clinical data suggest that well-differentiated pulmonary NET represent a distinct biologic entity [12]. Current systemic treatment options are of limited efficacy for patients with metastatic well-differentiated NET, and the prognosis is poor; median survival is 17 months and the 5-year survival rate is 27% [13]. This case report describes the long-term treatment of a woman with pulmonary well-differentiated NET and multiple liver metastases, including a favorable outcome from a novel systemic therapy.

Case Presentation

A 34-year-old white female patient was diagnosed in 1982 with well-differentiated pulmonary NET (TC). Upon seeking medical attention, she was asymptomatic, with an abnormality on radiographic examination. She underwent right lower pulmonary lobe resection, revealing TC arising from the bronchus. She did well until 1987, when she developed symptoms of flushing and was found to have metastatic disease to both pulmonary lobes and to the liver. She was then treated with octreotide long-acting repeatable (LAR) 20 mg monthly (table 1). The patient did well with good control of symptoms until 1998, when she developed increasing symptoms of flushing and had radiographic progression in the liver. Subsequently, sequential right and left hepatic lobe embolizations were performed, resulting in symptomatic improvement, a marked decrease in 5-hydroxyindoleacetic acid levels, and objective tumor regression. The disease and symptoms were controlled with octreotide LAR 30 mg monthly until July 2001, at which time treatment with octreotide LAR was discontinued and yttrium-90-labeled somatostatin (⁹⁰Y-somatostatin) was administered as part of a clinical trial. Three doses of ⁹⁰Y-somatostatin were administered over 3 months, the final dose in October 2001. Transient improvements in symptoms were noted without overt tumor response.

In May 2002, the patient had increased symptoms of flushing, fatigue, and diarrhea with progression in the liver. The same month, an exploratory laparotomy with 2 wedge resections and radiofrequency ablations of 6 tumors was performed. This resulted in a reduction in symptoms and in 5-hydroxyindoleacetic acid levels. Surgery was immediately

followed by resumption of octreotide LAR 30 mg monthly. In November 2006, octreotide LAR was increased to 40 mg monthly because of an increase in flushing; this treatment was associated with a subsequent improvement in this symptom.

In February 2007, and despite treatment with octreotide LAR, the patient developed increased abdominal distress and had at least 1 event of melena with a negative esophagogastroduodenoscopy result. Epigastric discomfort increased over the subsequent 5 months and, in June 2007, magnetic resonance imaging (MRI) of the liver showed progression of disease.

The patient was referred for the RAD001 in Advanced Neuroendocrine Tumors, Second Trial (RADIANT-2), in September 2007. All patients enrolled in RADIANT-2 provided written informed consent, and the RADIANT-2 protocol was approved by the institutional review board [14]. The patient's primary complaint was pain in the epigastrium, and examination was remarkable for painful hepatomegaly, with the liver descending 7 cm below the xiphoid process. The patient had iodine contrast allergy, and MRI of the liver revealed multiple bilateral tumors (fig. 1, fig. 2), several of which were measurable. Many smaller tumors were noted in a miliary pattern throughout both lobes of the liver.

The large phase III RADIANT-2 trial enrolled patients with advanced low-grade or intermediate-grade NET and a history of secretory symptoms (e.g. diarrhea and/or flushing) [14]. Patients were randomly assigned (1:1) to receive oral everolimus 10 mg once daily or matching placebo, both in combination with intramuscular octreotide LAR 30 mg every 29 days. The patient was randomly assigned to the everolimus plus octreotide LAR cohort. She reported prompt reduction in pain and resolution of painful hepatomegaly during the first few weeks of therapy. Radiographically, the liver remained stable over the course of the trial. Treatment was well tolerated without the most common adverse events associated with everolimus such as mucositis, rash, or pneumonitis. The patient had transient anemia and thrombocytopenia, which were thought to be treatment-related events. Intermittent elevations in creatinine improved with the discontinuation of diuretics and lisinopril. The patient remained on study over the course of 3 years. She showed symptomatic improvement as well as radiographic stability in liver lesions. In July 2010, the patient developed increasing pain in the epigastrium, renewed painful hepatomegaly, and elevations in transaminase and alkaline phosphatase levels. MRI showed progression in the liver. Upon termination of study participation, and in order to allow the patient to seek other trial options, treatment was unblinded and determined to be the everolimus plus octreotide LAR arm. Subsequently, she was treated sequentially with interferon and bevacizumab without response. The patient was referred for additional investigational therapy, but the level of liver dysfunction was exclusionary, and she subsequently received comfort care through the local hospice.

Discussion

Few published reports have described the long-term treatment of patients with advanced pulmonary NET. This may be attributed in part to the low incidence of the disease. However, given the dramatic increase in the incidence of pulmonary NET over the past few decades [13], insight into effective treatment of patients with this malignancy is of vital importance. This report describes the long-term treatment of a woman with pulmonary TC that metastasized to the liver. After all local and regional therapies had been exhausted, she enrolled in the RADIANT-2 study and was treated with everolimus plus octreotide LAR, which provided radiographic stability in the disease over 3 years. The patient experienced

symptomatic improvement over the same time course. Treatment was well tolerated by the patient, and mucositis, rash, and pneumonitis were not observed. Suspected treatment-related adverse events included transient anemia and thrombocytopenia. These adverse events are in line with those reported in previous trials of everolimus alone or in combination with octreotide LAR in patients with advanced NET [14–16].

The patient in this report achieved a clinical benefit with everolimus plus octreotide LAR that is consistent with results of the RADIANT-2 trial, which included patients with low- or intermediate-grade advanced NET; a subgroup analysis of patients in the RADIANT-2 trial with low- or intermediate-grade advanced pulmonary NET was also conducted. In the overall RADIANT-2 trial, treatment with everolimus plus octreotide LAR was associated with a median progression-free survival (PFS) of 16.4 months [95% confidence interval (CI), 13.7–21.2] [14]. In an exploratory subgroup analysis of 44 patients with low- or intermediate-grade advanced pulmonary NET in the RADIANT-2 trial, everolimus plus octreotide LAR treatment was associated with a median PFS of 13.63 months (95% CI, 5.55–14.29) [16]. The clinical benefit observed in this patient is encouraging because of the duration of time over which she exhibited stable disease, especially in light of her extensive pretreatment before receiving everolimus plus octreotide LAR.

Given the paucity of data on the treatment of patients with advanced pulmonary NET, results from an upcoming phase II clinical trial (LUNA, NCT01563354) will be of great interest. The multicenter 3-arm trial will evaluate the efficacy and safety of pasireotide LAR or everolimus alone or in combination in patients with well-differentiated neuroendocrine carcinoma of the lung and thymus. Estimated enrollment is 112 patients. The primary outcome is the proportion of patients who are progression free at 12 months. Secondary outcomes include PFS, disease control rate, time to response, duration of response, time to progression, biochemical response rate, and rate and severity of adverse events.

Everolimus is also being evaluated in combination with paclitaxel and carboplatin for the first-line treatment of patients with advanced large cell pulmonary cancer with neuroendocrine differentiation in a multicenter, open-label, phase II trial (NCT01317615). Estimated enrollment is 85 patients. The primary outcome is the proportion of patients who are progression free at 3 months. Secondary outcomes are the proportion of patients who are progression free at 6 months, overall response rate, disease control rate, PFS, and overall survival.

Finally, a phase III trial (RADIANT-4) will evaluate everolimus plus best supportive care versus placebo plus best supportive care in patients with advanced gastrointestinal or pulmonary NET (NCT01524783). Estimated enrollment is 285 patients. The primary outcome is PFS, and secondary outcomes include overall survival, objective response rate, disease control rate, changes in chromogranin A and neuron-specific enolase levels during the study, pharmacokinetics, time to definitive deterioration in World Health Organization performance status, health-related quality of life, and rate and severity of adverse events.

Results of these trials will expand the clinical body of evidence regarding the efficacy and safety of everolimus in patients with pulmonary NET. Everolimus is currently approved for the treatment of adults with progressive NET of pancreatic origin that is unresectable, locally advanced, or metastatic [17].

Conclusions

Treatment of patients with well-differentiated pulmonary NET refractory to resection can be challenging. This particular patient received most of the available treatment options

over the course of 25 years. Despite these efforts, her tumors continued to progress, and she experienced inconsistent relief of symptoms and significant pain associated with her tumors. Treatment with everolimus plus octreotide LAR in the RADIANT-2 trial produced a good clinical response and symptomatic improvement. Everolimus plus octreotide LAR represents an intriguing treatment option for the long-term treatment of patients with metastatic pulmonary carcinoid tumors.

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Ryan Mantooth has no competing interests.

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Table 1. History of management of functional pulmonary NET (TC) with octreotide LAR

Start date	End date	Dose	Symptoms	Outcome
April 1987	May 1998	20 mg monthly	Flushing	Good control of symptoms until 1998; symptom of flushing increased and patient had progression in the liver
May 1998	July 2001	30 mg monthly	Flushing	Octreotide LAR discontinued because of enrollment in clinical trial
May 2002	November 2006	30 mg monthly	Flushing	Good control of symptoms until November 2006; symptom of flushing increased
November 2006	September 2007	40 mg monthly	Flushing	Good control of symptoms until September 2007; patient reduced dose of octreotide LAR because of entry into RADIANT-2 trial
September 2007	July 2010	30 mg monthly	Flushing	Radiographically stable disease; improvement in nonmeasurable symptoms

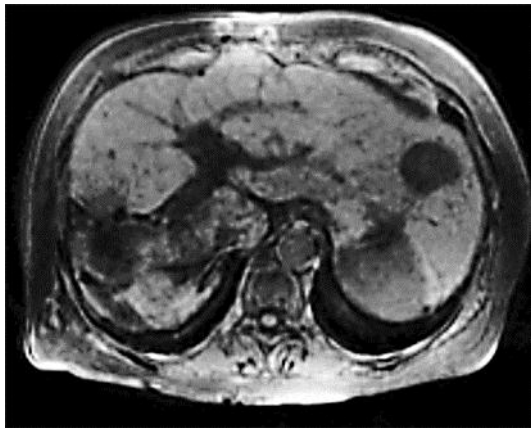


Fig. 1. MRI of the liver. September 2007, indicating multiple metastases.

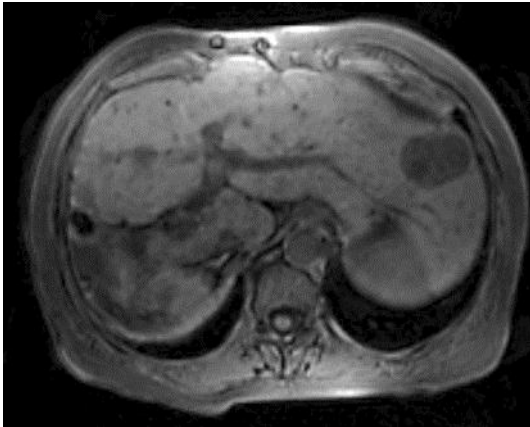


Fig. 2. MRI of the liver. September 2007, indicating multiple metastases.