



ENDOCRINOLOGÍA Y NUTRICIÓN

www.elsevier.es/endo



SCIENTIFIC LETTER

Three cases of sporadic medullary thyroid carcinoma in progression treated with sunitinib[☆]

Tres casos de carcinoma medular de tiroides esporádicos en progresión tratados con sunitinib

Medullary thyroid carcinoma (MTC) accounts for less than 5% of all thyroid carcinomas. Twenty-five percent of MTCs are familial in origin. Among apparently sporadic cases, 7–10% and 40–50% respectively have germinal and somatic mutations in the RET gene.¹ Ten-year survival is 65–75%. Surgery is the only curative treatment available. Radiotherapy and chemotherapy have a limited efficacy. A greater understanding of the role of angiogenesis and RET mutations has increased interest in tyrosine kinase inhibitors (ITKs).² In 2011, the FDA and EMEA approved the first ITK for the treatment of MTC in progression or symptomatic with non-resectable metastatic or locally advanced disease, vandetanib, and in 2012 the FDA also approved cabozantinib following favorable results in Phase III clinical trials.^{3,4}

The use of sunitinib for MTC was first reported in 2008.⁵ It is approved for use in gastrointestinal stroma, renal, and pancreatic neuroendocrine tumors, but favorable results in MTC have already been reported in Phase II trials.^{6–9}

Three patients with sporadic, progressing MTC were treated with sunitinib in a continuous scheme for compassionate use.

Case 1

A 63-year-old male was diagnosed with MTC based on fine needle aspiration (FNA) of an adenopathy. The patient consulted for dysphonia. Otolaryngological examination revealed an adenopathic conglomerate and left recurrent laryngeal nerve (RLN) palsy. A computed tomography (CT) scan revealed bilateral adenopathies and a mass in the left thyroid lobe (5.7 cm × 5 cm [APxT]) with coarse calcifications displacing and infiltrating the trachea and esophagus. Laboratory test results included calcitonin (CT) 910 pg/mL (NR, <19) and carcinoembryonic antigen (CEA) 6 ng/mL (NR, <5) with normal corrected calcium

(Ca), 25-hydroxyvitamin D (25OH-vitD), intact parathormone (iPTH), and metanephrine levels. Total thyroidectomy, emptying of the left central and cervical compartment and left resection of the RLN, parathyroid, and jugular vein (JV) were performed, leaving remnants in the esophagus and trachea. The pathological examination (PE) was reported as T3N1aMx.

The patient experienced syncope three months after surgery. Electrocardiogram and CT of the head were normal. CT decreased (410 pg/mL), and there were no changes in CEA. In the extension study, a CT scan showed left paratracheal remnants, a right adenopathic conglomerate, two bilateral pulmonary micronodules, and hypointense hepatic space-occupying lesions (hSOL) in segment IV (SIV) and SVI–SVIII with negative ¹¹¹In-pentetreotide (¹¹¹In-P) and bone ⁹⁹Tc-octetotide (⁹⁹Tc-O) scans. Surgery was ruled out due to high risk, and the oncology department suggested chemotherapy, but the patient preferred to wait. Six months later, the patient remained asymptomatic but showed increases in marker levels (CT/CEA 3178/58), adenopathic conglomerates (from 3.6 × 2.4 to 4 × 3 cm), and paratracheal and hepatic lesions (SVIII: from 1.6 to 2.5 cm). Because of progression, sunitinib 37.5 mg/d was started, causing grade 2–3 (according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0) hand–foot syndrome (HFS), grade 1–2 anemia and thrombocytopenia, and grade 2 asthenia. Sunitinib was therefore discontinued and restarted at 25 mg/d. One year later, tolerability had improved and decreases were found in markers and adenopathic conglomerates (1.7 cm), with hepatic and pulmonary stability. Treatment was therefore maintained.

Case 2

A 76-year-old male referred for multinodular goiter, dysphagia, and diarrhea (6–7 stools/d) who was diagnosed with MTC based on FNA of an adenopathy. He provided a ultrasound examination and a CT scan showing a 5-cm multinodular mass in the right thyroid lobe (RTL) entering the aortic arch, infiltrating and displacing the trachea and esophagus, and left latero-cervical and supraclavicular and right jugular adenopathies, a bronchoscopy showing an infiltrated and displaced trachea, and a normal gastrocolonoscopy. Laboratory test results included CT/CEA 11,640/548, iPTH 90 pg/mL (NR, 10–60), 25OH-vitD 18 ng/mL (NR, >30), and normal Ca, TSH, and metanephrines. Total thyroidectomy, jugulo-carotid and bilateral posterior triangle lymphadenectomy, esophageal myotomy, and RLN release were performed. PE was reported as pT3N1MO. One year later, dysphagia had improved but diarrhea and weight had

[☆] Please cite this article as: Currás Freixes M, Díaz Pérez JÁ, Casado Herráez A, Ochagavía Cámara S. Tres casos de carcinoma medular de tiroides esporádicos en progresión tratados con sunitinib. Endocrinol Nutr. 2014;61:62–63.

worsened, and bilateral supraclavicular adenopathies were confirmed in CT and ^{111}In -P scan with CT/CEA levels of 5,121/543 and negative bone ^{99}Tc -O. The somatostatin analog (SA) was started and bilateral supraclavicular lymphadenectomy confirmed the metastatic origin. Diarrhea and CT/CEA levels (2640/677) improved, while worsening occurred in dysphagia and weight. Imaging tests showed cervical and supraclavicular adenopathies, a mass extending from the surgical site to the mediastinum compressing the trachea and esophagus, and a hSOL in segment V. Palliative local radiotherapy was started, causing odynophagia and pneumonitis.

The patient's clinical status continued to worsen, with increases in CT/CEA levels (10,008/788) and mediastinal mass, and sunitinib 37.5 mg/d was started. In the following two years, the patient experienced an improvement in CT/CEA levels (1900/105) and clinical and radiographic signs which allowed for SA discontinuation and showed mild toxicity (HFS and grade 1–2 asthenia with poor blood pressure control). At the last follow-up, diarrhea and markers (CT/CEA 3680/138) had worsened and radiographic image remained stable. Either restarting SA or changing to vandetanib was under consideration.

Case 3

A 66-year-old male followed up at the gastroenterology department for biliary villous adenoma with severe dysplasia who underwent surgery in 2005. He was referred for elevated CEA levels (78 ng/mL) and uptake in laterocervical adenopathy and RTL in positron emission tomography (^{18}F FDG-PET). A CT scan of the abdomen and a colonoscopy were normal. Ultrasound examination and CT of the neck revealed laterocervical adenopathies infiltrating the JV, and the nodule in the RTL infiltrating the esophagus and trachea. FNA confirmed MTC. Laboratory test results included CT 987 pg/mL and normal Ca, 25OH-vitD, iPTH, and metanephrines. Total thyroidectomy and dissection of the left, central, and right lymph nodes including the JV was performed, leaving remnants in the esophagus. PE was reported as T3N1 Mx. Two months after surgery the patient remained symptom-free, but CT/CEA levels increased to 1,098/976. A CT scan showed a paraesophageal nodule and hypervascular hSOL in segment VIII. Magnetic resonance imaging and ultrasound-guided FNA confirmed a metastasis from MTC. The oncology and surgery departments were consulted, and doxorubicin 60 mg/m² in three doses was started. After chemotherapy, despite a decrease in CEA level (44 ng/mL) and radiographic stability of the paraesophageal nodule, the patient experienced increases in CT levels (2059 pg/mL) and in the size and number of hSOLs in segments VI–VIII with lung micronodules. Sunitinib 37.5 mg/d was started with poor tolerability (grade 2–3 HFS, grade 1–2 asthenia, anemia, and thrombocytopenia, and poor blood pressure control), and the dose was therefore reduced to 25 mg/d. Sixteen months after drug start, markers continued to decrease (CT/CEA 725/26) and radiographic stability was seen, but treatment was switched to oral sorafenib 200 mg/12 h due to poor tolerability. At two months, an abscess occurred at L4–L5 and the drug was temporarily discontinued. It was restarted with good tolerability. A worsening occurred in laboratory tests (CT/CEA 1659/64) and CT after two years with a pulmonary nodule, despite stability of the paraesophageal nodule and visualization of a single hSOL in segment VII. All three lesions showed uptake in ^{18}F FDG-PET/TC. Bronchoscopic studies were negative, and at a multidisciplinary session surgery was decided upon.

To sum up, we report the course of three patients with progressing MTC treated with ITKs due to a refusal of chemotherapy (case 1), refractoriness to the second surgery and radiotherapy (case 2) and chemotherapy (case 3). All three patients showed a favorable laboratory and radiographic response. All three patients experienced HFS, bicytopenia, and asthenia, and required adjustment of the levothyroxine dose, and two of them adjustment of antihypertensive doses. These adverse effects and gastrointestinal effects are very common.^{6–10} Infection, reported in only 1% of patients, occurred in case 2.

In conclusion, ITKs currently represent an alternative for the treatment of progressing MTCs.

References

1. De Groot JW, Links TP, Plukker JT, Lips CJ, Hofstra RM. RET as a diagnostic and therapeutic target in sporadic and hereditary endocrine tumors. *Endocr Rev*. 2006;27:535–60.
2. Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid*. 2009;19:565–612.
3. Wells Jr SA, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, et al. Vandetanib (VAN) in locally advanced or metastatic medullary thyroid cancer (MTC): a randomized, double-blind phase III trial (ZETA). *J Clin Oncol*. 2010;28(15S):5503.
4. Wells Jr SA, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol*. 2012;30:134–41.
5. Kelleher FC, McDermott R. Response to sunitinib in medullary thyroid cancer. *Ann Intern Med*. 2008;148:567.
6. De Souza JA, Busaidy N, Zimrin A, Seiwert TY, Villaflor VM, Poluru KB, et al. Phase II trial of sunitinib in medullary thyroid cancer (MTC). *J Clin Oncol*. 2010;28(15S):5504.
7. Cohen EE, Needles BM, Cullen KJ, Wong SJ, Wade JL, Ivy SP, et al. Phase 2 study of sunitinib in refractory thyroid cancer. *J Clin Oncol*. 2008;26(15S):6025.
8. Ravaud A, de la Fouchardière C, Asselineau J, Delord JP, do Cao C, Niccoli P, et al. Efficacy of sunitinib in advanced medullary thyroid carcinoma: intermediate results of phase II THYSU. *Oncologist*. 2010;15:212–3.
9. Carr LL, Mankoff DA, Goulart BH, Eaton KD, Capell PT, Kell EM, et al. Phase II study of daily sunitinib in FDG-PET-positive, iodine-refractory differentiated thyroid cancer and metastatic medullary carcinoma of the thyroid with functional imaging correlation. *Clin Cancer Res*. 2010;16:5260–8.
10. Cabanillas ME, Hu MI, Durand JB, Busaidy NL. Challenges associated with tyrosine kinase inhibitor therapy for metastatic thyroid cancer. *J Thyroid Res*. 2011;2011:985780.

Maria Currás Freixes^{a,*}, José Ángel Díaz Pérez^a,
Antonio Casado Herráez^c, Santiago Ochagavía Cámara^b

^a *Servicio de Endocrinología y Nutrición, Hospital Clínico San Carlos, Madrid, Spain*

^b *Servicio de Cirugía General, Hospital Clínico San Carlos, Madrid, Spain*

^c *Servicio de Oncología, Hospital Clínico San Carlos, Madrid, Spain*

*Corresponding author.

E-mail address: mariacufr@hotmail.com

(M. Currás Freixes).