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Original Research

Antitumour activity of somatostatin analogues in sporadic, progressive, metastatic pulmonary carcinoids

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Abstract ***Purpose:*** Antiproliferative activity of somatostatin analogues (SSAs) has been demonstrated in digestive neuroendocrine tumours but few data have been published on pulmonary carcinoids (PC). The aim of this retrospective study was to report the antitumour activity of SSAs in patients with progressive, metastatic PC.
Methods: Patients with PC and treated with SSA monotherapy were reviewed. Disease was classified according to the tumour slope prior to SSA initiation as rapidly progressive (at least 20% increase in the sum of the longest diameter of target lesions or the appearance of one or more new lesions within 6 months) or slowly progressive (if progression occurred over 6 months). Survival outcomes were progression-free survival (PFS) and overall survival (OS). We additionally examined the overall response rate and safety. Prognostic factors associated with PFS and OS were sought. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox model.
Results: Among 67 patients reviewed, 61 were included in the study. Forty-one (67%) of them exhibited slowly progressive disease prior to SSAs, 41 (67%) had atypical carcinoids and 29 (48%) had functioning tumours. Forty-six (76%) patients had received SSAs as first-line

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therapy. The best overall response was stable disease in 47 (77%) patients. The median duration of SSAs was 13.7 months. With a median follow-up of 5.8 years, median PFS and OS were 17.4 (95% CI: 8.7–26.0) and 58.4 (95% CI: 44.2–102.7) months, respectively. Functioning tumours and slowly progressive disease were significantly associated with longer PFS: HR = 0.48 ([95% CI: 0.24–0.95], $p = 0.03$) and HR = 7.43 ([95% CI: 3.02–18.25], $p < 0.0001$), respectively. Only functioning tumours remained significantly associated with OS: HR = 0.33 ([95% CI: 0.14–0.79], $p = 0.01$). Treatment had been discontinued in two patients due to side-effects.

Conclusions: Median PFS observed in our study is encouraging for PC patients. Patients with functioning tumours and slowly progressive disease treated with SSAs have better prognosis.

1. Introduction

Neuroendocrine tumours (NETs) are rare epithelial neoplasms with neuroendocrine differentiation that most commonly originate in the lungs and gastrointestinal tract. Pulmonary NETs represent approximately 25% of primary lung neoplasms and 20–25% of primary NETs [1–3]. The 2015 World Health Organisation (WHO) classification recognises four major types of pulmonary NETs: in the spectrum of low-grade tumours, typical (TC) and atypical carcinoids (AC) and small-cell carcinomas and large-cell neuroendocrine carcinomas among the high-grade tumours [4]. Pulmonary carcinoids (PC) account for 1–2% of all invasive lung malignancies and their incidence has increased over the past 30 years, possibly due to improvements in histological diagnostic tools, as well as to the major diffusion of lung cancer screening programs worldwide [1–3,5]. While surgery is the mainstay of treatment for localised lesions, no standard systemic therapies have been established for advanced/unresectable disease, and most of them are extrapolated from gastro-enteropancreatic (GEP)-NETs. Symptoms related to hormone secretion are present in approximately 40% of advanced PC with carcinoid syndrome being the most common [6,7]. Medical management aims to control both, hormone-related symptoms and tumour growth [8,9]. Somatostatin analogues (SSAs) were first introduced to control hormone-mediated symptoms but their antiproliferative activity was demonstrated in multiple prospective and retrospective studies that included PC [10–12].

The antitumour activity of octreotide and lanreotide was finally demonstrated in two pivotal phase III trials, which included mainly ileum G1 NETs or slowly progressive digestive NETs [13,14]. The European Neuroendocrine Tumor Society recently released an expert consensus document to provide guidance on the management of PC [9]. Treatment options for patients with advanced TC or slowly progressive disease are a 'watch and see strategy', SSAs or image-guided local therapy. In patients with AC or rapidly progressive disease, everolimus, interferon, peptide receptor radionuclide therapy or chemotherapy (e.g. temozolomide) are considered as options. The first randomised, phase II three-arm trial, analysing the antitumour efficacy and safety of everolimus or pasireotide alone or in combination (ClinicalTrial.gov: NCT01563354), entirely dedicated to patients with advanced carcinoids of the lung and thymus has been completed (LUNA trial) and the results are expected in 2016.

The objective of this retrospective study was to report the antitumour activity of SSA monotherapy in patients with sporadic, progressive, metastatic PC.

2. Material and methods

2.1. Study population

From January 1986 to March 2015, all patients with sporadic metastatic PC and treated with SSA monotherapy at Gustave Roussy (Villejuif, France), were retrospectively reviewed. Inclusion criteria were: (a) a histopathological confirmed diagnosis of PC according to 2004 WHO criteria [4] (for patients diagnosed before 2004 a pathological review was carried out); (b) documented progressive metastatic disease according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 before starting SSAs [15]; (c) Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–2 and (d) at least one tumour response evaluation under SSAs.

The following data were collected by a single investigator from electronic medical records: (1) at diagnosis; age, gender, tobacco exposure, histological subtype, Ki-67 index (cut-off following a recent proposal [16]), number of mitoses, primary tumour site, TNM/AJCC (tumour-node-metastasis/American Joint Committee on Cancer 2010 stage) [17] and (2) prior to the initiation of SSAs; age, ECOG PS, surgery of primary tumour, functional tumour status, number of previous lines of systemic treatments, slope of tumour progression (progression defined according to RECIST v1.1) to classify the disease as rapidly progressive if at least 20% increase