Lung Cancer 96 (2016) 68–73

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Evaluation of the combination of oxaliplatin and 5-fluorouracil or gemcitabine in patients with sporadic metastatic pulmonary carcinoid tumors

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ARTICLE INFO

Article history:
Received 16 February 2016
Received in revised form 30 March 2016
Accepted 30 March 2016

Keywords:
Chemotherapy
Gemox
Folfox
Carcinoid
Pulmonary
Lung

ABSTRACT

Objectives: The aim of this retrospective study was to analyse the efficacy of gemcitabine-oxaliplatin (gemox) or 5-fluorouracil-oxaliplatin (folfox) in the treatment of metastatic pulmonary carcinoid tumors.
Patients and methods: 45 patients were included in two tertiary referral centers between January 1999 and January 2013. Typical, atypical carcinoids or not otherwise specified carcinoids were diagnosed according to WHO criteria in 19%, 57%, and 24% of cases by two expert pathologists. Patients had synchronous (38%) or metachronous (62%) metastatic disease (median of 2 (1–5) metastatic sites). Seventy-nine percent had progressive disease before start of chemotherapy. Treatment consisted of: gemcitabine 1000 mg/m^2 and oxaliplatin 100 mg/m^2 every 2 weeks (gemox regimen, n = 24) or 5-fluorouracil (5-FU) (400 mg/m^2 in bolus injection and 5-FU 2400 mg/m^2 in 46 h-infusion) and oxaliplatin 85 mg/m^2 (folfox regimen, n = 21) every 2 weeks. Tumor response was assessed according to RECIST criteria every 8–12 weeks. Progression free survival and overall survival were assessed using Kaplan Meier curves.
Results: Patients received oxaliplatin-based chemotherapy in first-line (20%), second-line (33%), or post-second-line (47%) systemic treatment. The median number of cycles was 8 (1–12). Nine (20%) stopped oxaliplatin before 8 cycles because of toxicity. Nine patients (20%) had a partial response and 29 (64%) had stable disease. Median progression free survival (PFS) was 15 (6–25) months. Median overall survival (OS) was 34 (21–49) months. No significant difference was observed in response and PFS between either regimens.
Conclusions: Our results suggest that either gemcitabine-oxaliplatin or 5-fluorouracil-oxaliplatin combinations are attractive chemotherapy regimen in metastatic pulmonary carcinoid tumors.
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1. Introduction

Neuroendocrine tumors (NETs) are rare, but their incidence is rising [1]. The bronchopulmonary system is their second most frequent primary location (25% of cases) [1,2]. The 2015 WHO pathological classification recognizes 4 subtypes of pulmonary NETs [3]. Two are well differentiated tumors: typical carcinoid (TC) and atypical carcinoid (AC). Two are poorly differentiated carcinomas: large cell neuroendocrine carcinoma and small cell neuroendocrine carcinoma. TC represents 80–90% of pulmonary

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http://dx.doi.org/10.1016/j.lungcan.2016.03.018
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carcinoid tumors [4]. They are usually localized with synchronous metastatic dissemination in only 5–20%, whereas AC exhibit more often lymph node involvement and distant metastatic disease. First line treatment is surgery but, unfortunately, 28–34% pulmonary carcinoid tumors are diagnosed at advanced, unresectable stages [1,5].

Guidelines from European Neuroendocrine Tumor Society (ENETS) for the treatment of metastatic pulmonary carcinoid tumors were recently reported [6]. In patients with TC or slow growing tumors: a watch and see strategy, somatostatin analogs or locoregional imaging guided therapies (radiofrequency ablation and transarterial embolization of liver metastases) were considered as options. In patients with AC or rapidly progressive tumors: everolimus [7], peptide receptor radionuclide therapy or cytotoxic chemotherapy were considered as options. However, the paucity of data and the urgent need for studies dedicated to the field pulmonary carcinoids were mainly emphasized.

Cytotoxic chemotherapy is the standard first line treatment for advanced poorly differentiated neuroendocrine carcinoma, but also for advanced well-differentiated pancreatic NETs, in which response rates of 30–40% and median progression free survivals of 4–18 months have been reported [8–12]. Two main options exist for systemic chemotherapy in well differentiated NETs: alkylating agents, including streptozocin, dacarbazine, and temozolomide, or oxaliplatin-based combinations. Little data are available about these treatments in pulmonary carcinoids. Only temozolomide has been shown to result in clinical benefit in this localization [13–15]. Oxaliplatin combined with either 5-fluouracile [16–19] or gemcitabine [20,21] has shown interesting activity with response rates between 17 and 30% in several NET subsets [16,20–23], including pulmonary carcinoid tumors.

We were therefore prompted to design a retrospective study to assess the efficacy of the combinations oxaliplatin-gemcitabine (gemox) and oxaliplatin-5-fluorouracile (folfox) in patients with aggressive metastatic pulmonary carcinoid tumors.

2. Patients and methods

2.1. Study population

Consecutive patients with a metastatic pulmonary carcinoid tumor treated by oxaliplatin-based chemotherapy referred to two tertiary referral center (E Herriot Hospital (Lyon, France, ENETS center of excellence) and Gustave Roussy (Villejuif, France, French center of excellence)) between January 2000 and January 2013 were included in this retrospective study. Inclusion criteria were a) a confirmed pathology diagnosis of pulmonary carcinoid tumors by expert pathologists (V.H., P.D. and J-Y.S.), classifiable according to World Health Organization (WHO) criteria; b) performance status 0–2 and normal cardiac, renal, liver, and blood cell functions and blood count; c) recovery from toxic effects of previous chemotherapy; d) at least one cycle of gemox of folfox chemotherapy. They may have received previous lines of systemic treatments, such as somatostatin analogs, interferon, everolimus, cytotoxic chemotherapy and/or peptide receptor radionuclide therapy.

The following data were collected: number of previous lines, disease progression before treatment, type of regimen, start and end date of chemotherapy, number of cycles, and efficiency: best response assessed with RECIST 1.0 criteria (objective response (OR); stable disease (SD) defined as disease stable for at least 2 months of treatment; progressive disease (PD)), progression free survival (PFS), and overall survival (OS). Patients were assessed at 2–3 month intervals of treatment, depending on physician's choice. To look for prognostic parameters, we also collected: age, gender, performance status, typical versus atypical carcinoid defined according to the WHO criteria for lung tumors, Ki67 index reported according to the grading system proposed by the WHO classification of digestive NETs system, number and localization of metastatic sites, functional tumor status, and uptake at somatostatin receptor scintigraphy (SRS) or FDG PET status as categorized in Table 1.

2.2. Chemotherapy regimens

Two chemotherapy regimens were used, both administred every 2 weeks:

- the GEMOX regimen was only used at Edouard Herriot Hospital and consisted of gemcitabine 1000 mg/m^2 as a 30 min intravenous infusion followed by oxaliplatin 100 mg/m^2 as a 2 h intravenous infusion [20,21].
- the FOLFOX regimen was mainly used at Gustave Roussy and consisted of a 2 h-infusion of oxaliplatin 85 mg/m^2, a 2 h-infusion of leucovorin 400 mg/m^2, 5-fluorouracil (5-FU) 400 mg/m^2 as a 10 min bolus injection, and 5-FU 2400 mg/m^2 as a 46 h-infusion [22].

Chemotherapy was usually stopped at the end of 8 cycles in case of disease control, in order to avoid severe neurotoxicity; dose reduction was performed according to guidelines.

2.3. Statistical analysis

Categorical variables were expressed as percentages, and compared by the Chi-square test or with Fisher's exact test when appropriate. Continuous variables were expressed as median with range. The PFS was calculated from initiation of treatment to the date of disease progression according to RECIST 1.0 criteria or death from any cause, whichever occurred first. The OS was calculated from initiation of treatment to the date of death or last follow-up. The PFS and the OS were assessed using Kaplan–Meier analysis and comparisons were performed using the log-rank test. A P value of <0.05 was considered statistically significant. Cox proportional hazard models were developed using relevant clinic-pathologic variables to determine the association of each parameter with OS or PFS. For continuous variables, the cut-off level chosen was their median value. Only variables with a P value of <0.10 at univariate analysis were introduced in the Cox model. Relative risks were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). The cut-off date for the final analysis was July 1, 2014. All statistical analyses were performed using Statistical Package for Social Sciences version 17.0 (Chicago, IL).

3. Results

3.1. Study population

Forty-five patients treated with oxaliplatin-based chemotherapy for metastatic pulmonary carcinoid tumor were included in our study group (25 from Lyon and 20 from Villejuif). Clinical characteristics are summarized in Table 1: 19 patients were male; median age was 57 years; 37 patients (92%) had a performance status 0–1; 42% of patients were functioning. Tumor SRS or FDG uptake were positive in 23/30 (77%) or13/14 (93%) patients. Metastases were synchronous in 38% of patients. The median number of metastatic sites was 2 (range, 1–5). According to the WHO classification of pulmonary NETs, most tumors were classified as atypical carcinoid (57%); the final classification could not be achieved in 10 (24%) patients, because only biopsy samples from a metastatic

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