European Journal of Cancer 79 (2017) 158–165

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Poorly differentiated gastro-entero-pancreatic neuroendocrine carcinomas: Are they really heterogeneous? Insights from the FFCD-GTE national cohort

T. Walter [a,*], D. Tougeron [b], E. Baudin [c], K. Le Malicot [d], T. Lecomte [e], D. Malka [c], O. Hentic [f], S. Manfredi [g], I. Bonnet [h], R. Guimbaud [i], R. Coriat [j], C. Lepère [k], C. Desauw [l], A. Thirot-Bidault [m], L. Dahan [n], G. Roquin [o], T. Aparicio [p], J.-L. Legoux [q], C. Lombard-Bohas [a], J.-Y. Scoazec [c], C. Lepage [d,r,1], G. Cadiot [s,1], For the CEPD investigators[2]

[a] *University Hospital, Lyon, France*
[b] *University Hospital, Poitiers, France*
[c] *Gustave Roussy Institute, Villejuif, France*
[d] *FFCD, Dijon, France*
[e] *Trousseau Hospital, Tours, France*
[f] *Beaujon Hospital, Clichy, France*
[g] *University Hospital, Rennes, France*
[h] *Valenciennes Hospital, Valenciennes, France*
[i] *University Hospital, Toulouse, France*
[j] *Cochin Hospital, University Paris Descartes, Paris, France*
[k] *Georges Pompidou European Hospital, University Paris-V, Paris, France*
[l] *University Hospital, Lille, France*
[m] *Hôpitalde Bicêtre, Le Kremlin Bicêtre, France*

* *Corresponding author*: Department of Medical Oncology (Pavillon E, UJOMM), Edouard Herriot Hospital, Lyon 69003, France. Fax: +33 4 72 11 96 91.
E-mail address: thomas.walter@chu-lyon.fr (T. Walter).

[1] Equally contributed.

[2] **List of Investigators/Collaborators:** Dr. Laetitia Stephanie (Centre Hospitalier, Annecy); Dr. Ivan Borbath (Cliniques Universitaires Saint Luc, Bruxelles); Dr. Castex (CHU Robert Debré, Reims); Dr. Caroline Petorin (CHU d'Estaing, Clermont Ferrand); Dr. Eric Terrebonne (Hôpital Haut Lévèque, Bordeaux); Dr. Karine Bouhier-Leporrier (CHU Côte de Nacre, Caen); Dr. Etienne Suc (Clinique Privée Saint Jean Languedoc, Toulouse); Dr. Vincent Hautefeuille (CHU Amiens, Amiens); Dr. Vincent Bourgeois (CH Duchenne, Boulogne sur Mer); Dr. Laurent Cany (Polyclinique Francheville, Périgueux); Dr. François Dewaele (Centre Catherine de Sienne, Nantes); Dr. Patricia Niccoli (CHU La Timone, Marseille); Pr. Jean-François Seitz (CHU La Timone, Marseille); Dr. Cédric Lecaille (Polyclinique Bordeaux Nord, Bordeaux); Pr. Christine Rebischung (CHU A. Michallon, Grenoble); Dr. Valérie Rossi (CH du Haut Anjou, Château-Gontier); Dr. Mathieu Baconnier (CH Annecy Genevois, Annecy); Dr. Olivier Dubreuil (Groupe hospitalier Pitié-Salpétrière, Paris); Dr. Marc Ferec (Centre Hospitalier du pays de Morlaix, Morlaix); Dr Gael Deplanque (Hôpital Paris St Joseph, Paris); Dr. Guillaume Geslin (Cabinet privé des Dr. Geslin Provost, Vannes); Dr. Isabelle Wanicki Caron (CHU Charles Nicolle, Rouen); Dr. Sandrine Lavau Denes (CHU Dupuytren, Limoges); Pr. Laurent Bedenne (CHU Le Bocage, Dijon); Dr. Catherine Ligeza (Clinique Mutualiste de l'Estuaire, Saint Nazaire); Dr. Eric Maringe (Centre Hospitalier de Beaune, Beaune); Dr. Anne-Laure Ran-Royo (Centre de radiothérapie et d'oncologie médicale privée, Béziers); Dr. Joel Guigay (Unicancer Nice); Pr. Philippe Rougier (HEGP, université Paris-V, 75015 Paris).

http://dx.doi.org/10.1016/j.ejca.2017.04.009

[n] La Timone Hospital, Marseille, France
[o] University Hospital, Angers, France
[p] Avicenne Hospital, Bobigny, France
[q] Hôpital de la Source, Orléans, France
[r] University Hospital, Dijon, France
[s] University Hospital, Reims, France

Received 14 September 2016; received in revised form 5 April 2017; accepted 6 April 2017
Available online 11 May 2017

KEYWORDS
Gastrointestinal cancer;
Neuroendocrine carcinoma;
Ki67 index;
Prognosis;
Treatment

Abstract ***Background:*** Diagnosis and management of poorly differentiated gastro-entero-pancreatic (GEP) neuroendocrine carcinomas (NECs) remain challenging. Recent studies suggest prognostic heterogeneity. We designed within the French Group of Endocrine Tumours a prospective cohort to gain insight in the prognostic stratification and treatment of GEP-NEC.

Patients and methods: All patients with a diagnosis of GEP-NEC between 1st January 2010 and 31st December 2013 could be included in this national cohort. Adenoneuroendocrine tumours were excluded.

Results: 253 patients from 49 centres were included. Median age was 66 years. Main primary locations were pancreas (21%), colorectal (27%), oesophagus-stomach (18%); primary location was unknown in 20%. Tumours were metastatic at diagnosis in 78% of cases. Performance status (PS) at diagnosis was 0–1 in 79% of patients. Among the 147 (58%) cases reviewed by an expert pathological network, 39% were classified as small cell NEC and 61% as large cell NEC. Median Ki67 index was 75% (range, 20–100). Median overall survival was 15.6 (13.6–17.0) months. Significant adverse prognostic factors in univariate analysis were PS > 1 (hazard ratio [HR] = 2.5), metastatic disease (HR = 1.6), NSE > 2 upper limit of normal [ULN]; HR = 3.2), CgA > 2 ULN (HR = 1.7) and lactate dehydrogenase >2 ULN (HR = 2.1). After first-line palliative chemotherapy (CT1) with platinum-etoposide (n = 152), objective response, progression-free survival and overall survival were 50%, 6.2 and 11.6 months; they were 24%, 2.9 and 5.9, respectively, after post-CT1 FOLFIRI regimen (n = 72).

Conclusions: We report a large prospective series of GEP-NEC which show the predominance of large cell type and advanced stage at diagnosis. Prognosis was found more homogeneous than previously reported, mainly impacted by PS and tumour burden.

1. Introduction

Gastro-entero-pancreatic neuroendocrine carcinomas (GEP-NECs) are defined as carcinomas showing neuroendocrine marker expression, poorly differentiated morphology and high proliferative capacities (grade 3) [1]. Two histological types, small cell and large cell, are distinguished by the current World Health Organisation (WHO) classification of GEP neuroendocrine neoplasms [2]. GEP-NECs are the most frequent NECs [3–5], once small cell lung carcinoma is excluded. The spontaneous prognosis of GEP-NECs is poor, with a median survival in the absence of treatment of 6–7 months [4]. By contrast with well-differentiated neuroendocrine tumours (NETs), GEP-NECs require urgent systemic chemotherapy that combines platinum salts (cisplatin or carboplatin) with etoposide. NECs are quite sensitive to chemotherapy, with partial response rate ranging from 40% to 75% [6–8]. However, the median duration of treatment response is only 8–9 months, and the almost inevitable onset of secondary resistance leads to a median overall survival (OS) of 15–18 months under chemotherapy. When tumour relapse or progression is observed, second-line chemotherapy with platinum-etoposide is an option in sensitive cases; alternatively, treatments including FOLFIRI, FOLFOX or temozolomide-based chemotherapies have been proposed [6,9–11].

A number of issues regarding GEP-NECs remain to be adequately addressed. Their epidemiology is not well stated. The incidence of GEP large cell NEC increased the last two decades whereas the incidence of GEP small cell carcinoma was unaltered [5]. However, it is unclear