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Intervention in gastro-enteropancreatic neuroendocrine tumours

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A B S T R A C T

Neuroendocrine tumours require dedicated interventions to control their capacity to secrete hormones but also, antitumour growth strategies. Recommendations for early interventions in NET include the management of hormone-related symptoms and poorly differentiated neuroendocrine carcinomas. In contrast, prognostic heterogeneity is a key feature of well differentiated NET that complexified the antitumour strategy whatever the stage in this subgroup of tumour. In this review, timely therapeutic interventions to control hormone-related symptoms and tumour growth in GEP NET patients are discussed. The necessity of

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controlling hormone-related symptoms as the first step of any strategy affects also the tumour growth control strategy. In the absence of cure at the metastatic stage, progresses are expected in the recognition of well differentiated NET subgroups that display either excellent or poor prognosis.

Introduction

Gastro-enteropancreatic neuroendocrine tumours (GEP NET) constitute a heterogeneous group of tumours responding to a common definition i.e. the expression of specific markers associated with the granules and vesicules characteristic of peptide-producing neuroendocrine cells. They also express common characteristics, including the secretion of hormones, their association as part of inherited syndromes, the existence of common activated molecular pathways but also the expression of specialized membrane receptors like the somatostatin receptors, the presence of a hypervascularized stroma [1,2]. These characteristics translate into a common characterization process but also into common therapeutic targeting [3]. The primary location but also the pathological differentiation, recently incorporated along with the proliferative capacities as part of grading for digestive NET, strongly influence their presentation but also correlate with the stage at diagnosis [1,4–15] (Table 1).

Although NETs were initially thought to pursue an indolent course, successive standardization of pathological and TNM classifications were of major help in outlining the prognostic heterogeneity of this group of tumours. Indeed, even at the metastatic stage, survival ranges between 0 and 100% at five years according to the characteristics of the tumour. In the absence of curative tools at this advanced stage [16] and due to the fact that a large number of randomized trials have not been carried out, prognostic parameters balanced with safety issues remain the decisive elements of the antitumour therapeutic intervention, nowadays.

In this review, the term well differentiated neuroendocrine tumour will apply to G1 and G2 digestive NET but also to typical and atypical bronchial carcinoids. Poorly differentiated neuroendocrine tumour will apply to G3 digestive NEC but also to large cell bronchial carcinoma. The issue of small cell lung carcinoma will not be specifically addressed. Data issued from expert centres, that provide a multivariate analysis, constitute the basis of this review since they provide the most comprehensive and standardized characterization of patients. We will discuss therapeutic interventions to control hormone-related symptoms first and then, tumour growth in GEP NET patients and show how the necessity of controlling hormone-related symptoms as the first step of any strategy affects the tumour growth control strategy.

Intervention in GEP NET for the control of hormone-related symptoms

Functioning syndrome a typical feature of well differentiated NET

One of the most specific features of NETs in oncology is their ability to secrete hormones, creating hormone-related symptoms, also named functioning syndromes. The presence of hormone-related

Table 1
Primary location as a function of presence of distant metastasis and probability of poorly differentiated carcinoma at diagnosis.

TNM stage at diagnosis	Pathological differentiation-grading	
	Probability of poorly differentiated carcinoma $\leq$1%	Probability of poorly differentiated carcinoma >1%
Distant metastasis <15%	Appendix Insulinoma-gastrinoma	Bronchus Rectum Gastric
Distant metastasis >15%	Ileum Other functioning pNET	Pancreas (non-functioning)

pNET = pancreatic neuroendocrine tumour.