Neuroendocrine tumors: insights into innovative therapeutic options and rational development of targeted therapies

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Neuroendocrine tumors (NETs) are heterogeneous neoplasms with respect to molecular characteristics and clinical outcome. Although slow-growing, NETs are often late diagnosed, already showing invasion of adjacent tissues and metastases. Precise knowledge of NET biological and molecular features has opened the door to the identification of novel pharmacological targets. Therapeutic options include somatostatin analogs, alone or in combination with interferon-α, multi-targeted tyrosine kinase inhibitors (e.g. sunitinib) or mammalian target of rapamycin (mTOR) inhibitors (e.g. everolimus). Antiangiogenic approaches and anti insulin-like growth factor receptor (IGFR) compounds have been also proposed as combination therapies with the aforementioned compounds. This review will focus on recent studies that have improved therapeutic strategies in NETs, discussing management challenges such as drug resistance development as well as focusing on the need for predictive biomarkers to design distinct drug combinations and optimize pharmacological control.

Introduction

Over the past decade, molecular and cellular biology studies have radically modified our knowledge of neuroendocrine tumor (NET) biology, pathogenesis and management [1]. NETs derive from neuroendocrine cells of the diffuse endocrine system and represent a heterogeneous group of neoplasms. NETs can arise almost anywhere in the body and are therefore associated with a broad range of local and systemic symptoms related to mass effects and/or to the secretion of numerous hormones and biogenic amines [1,2].

Although often described as rare, the incidence of NETs has shown a marked increase over the past three decades [3,4]. The Surveillance, Epidemiology and End Result Registry (SEERR) has shown that NET incidence in the USA increased fivefold from 1973 to 2004 (from one to five per 100,000 individuals) [2,3,5,6]. This finding probably depends on an increase in incidental diagnoses in patients with few or no symptoms secondary to improved clinical awareness, widespread use of cross-sectional imaging and endoscopic techniques, as well as plasma biomarker measurement and more-accurate histopathological diagnosis as a result of immunohistochemistry [2,3,5]. NET prevalence (35 in 100,000 in 2004), by contrast, is much higher than incidence because of the long-ranging survival of many patients [6]. In fact, considering all gastroenteropancreatic (GEP) NETs together, these tumors represent the second neoplasm for prevalence of the gastrointestinal (GI) tract, following colon adenocarcinoma [4].

In terms of site of origin, NETs occur most commonly in the GI tract (about 70%) and bronchopulmonary system (about 25%), although this number is likely to be underestimated because nonmalignant lesions are not included in the SEERR [7]. Accordingly, lung, small intestinal and rectal NETs show the highest incidence rates [4]. If we consider all epithelial malignancies of the GI tract and lung, NETs represent 2% for each [7]. Whereas general neuroendocrine features are shared by all neoplasms, some clinical and pathological aspects are specific to the organ of origin [8].

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With regard to nomenclature, the term carcinoid has been repeatedly criticized because of existing concerns that it might not adequately convey the potential malignant behavior of many of these neoplasms. For this reason, in the 2000s, the term was dropped for more-appropriate definitions (such as endocrine or neuroendocrine, tumor or carcinoma), which in turn evolved in different subsequent classifications. The term carcinoid tumor, however, remains in use in a few selected cases; for example in the official WHO classification of lung NETs, to indicate carcinoid syndrome and, unfortunately, in many studies and clinical trials to indicate the NETs of GI origin [8]. During the past 20 years, the histological classification of NETs has also undergone two important modifications to more closely correlate with clinical outcome. The most relevant criteria for prognostic stratification of patients were shown to be differentiation, identified in the 2000 WHO classification, and a proliferation-based grading system, introduced by the European Neuroendocrine Tumor Society (ENETS) and incorporated into the 2010 WHO classification of tumors of the digestive system [9]. Differentiation allows the identification of two distinct prognostic groups: well differentiated (WD) and poorly differentiated (PD) neoplasms (Table 1). Although the latter group comprises biologically aggressive neoplasms and follows an unfavorable clinical course, the WD group comprises tumors that can be completely cured or can permit long-term survival even in the presence of relapse or metastasis. Histology alone, however, is unable to distinguish relevant prognostic categories within this group. In consideration of this drawback, initially ENETS [10,11], and WHO later on, introduced a grading system based on proliferation index thereby subdividing NETs into low, intermediate and high grades (G1, G2 and G3, respectively). Mitotic rate (number of mitoses per ten high-power microscopic fields; HPF) and proliferative index (% of tumor cells positive by immunohistochemistry for the proliferation marker Ki-67; Ki-67 index) are both concomitantly used for grade determination (Table 1). The ENETS and UICC have also introduced a staging system based on the widespread TNM system.

Whether Ki-67 is the gold standard for prognostic evaluation is however still debated. Inherent problems are: (i) the exact areas and methods of evaluation are ill defined; (ii) the intermediate category (G2) is still too broad; and (iii) better cut-off of percentages that separate grades still has to be identified for some sites. Although Ki-67 is not considered a predictive parameter, it can however guide the choice of therapy identifying tumors with high proliferative index that might require chemotherapy [12]. New prognostic factors are eagerly awaited, among these cycle markers [13] or other proteins (CK19, CD117, CD99, etc.) have recently been the object of analysis.

NETs: from standard treatments to innovation therapy

As first-line treatment, localized tumors or NETs showing only regional spread require surgery with either radical or cytoreductive intent, probably able to relieve symptoms even of metastatic and/or high-grade NETs. In the case of metastatic NETs (about 85% of all NETs) [2], medical treatment is recommended and very much needed although a real adjuvant and/or neoadjuvant setting has still not been defined by randomized trials. The current medical treatment for locally advanced or metastatic G1/G2 NETs includes somatostatin (SRIF) analogs (SSAs), interferon-α (IFN-α), radionuclide (^{90}Y or ^{177}Lu) coupled SSAs and, more recently, targeted therapies. Cytotoxic chemotherapy has been mainly used in patients with highly proliferating NETs (G3), and in particular some pancreatic and lung NETs [14]. Cisplatin/etoposide combination is considered a first-line treatment for G3 tumors, although its efficacy is controversial, and different response rates have been reported. In G2 tumors, mainly pancreatic, a combination of streptozotocin and 5-fluorouracil is provided by all international guidelines for NETs. Alternatively, carboplatin/irinotecan, gemcitabine or oxaliplatin are also used [15]. Furthermore, temozolomide, alone or in association with capecitabine, was promising in terms of antitumor effect and toxicity in certain series of lung and pancreatic NETs [16,17]. Complementary loco-regional or ablative therapies are used to treat liver metastases.

Considering the very high rate of patients with synchronous metastases at diagnosis, and therefore unsuitable for surgery, and the typical indolent growth of these tumors allowing long survival even in advanced stages of disease, it has become very important to find more-effective medical therapy. In this context, the development of targeted therapies for NETs is of extreme interest for the effectiveness so far demonstrated in this particular category of neoplasms and for the general good tolerability profile of these drugs, compared, for example, with classical chemotherapy regimens. Indeed, NET patients, who have long survival and therefore

TABLE 1

Pathologic classification of neuroendocrine tumors: nomenclature and grading systems

WHO 1980	WHO 2000	WHO 2010			
			Grade	Mitosis/10HPF[a]	Ki-67 index[b] (%)
Carcinoid	Well differentiated endocrine tumors (WDET)	NET	G1 (low)	<2	≤2
	Well differentiated endocrine carcinoma (WDEC)		G2 (intermediate)	2–20	3–20
	Poorly differentiated endocrine carcinoma/small cell carcinoma (PDEC)	NEC	G3 (high)	>20	>20
Mucocarcinoid **Mixed forms carcinoid-adenocarcinoma**	Mixed exocrine/endocrine carcinoma (MEEC)	Mixed adeno-neuroendocrine carcinoma (MANEC)			
Pseudotumor lesions	Tumor-like lesion (TLL)	Hyperplastic and preneoplastic lesions			

Modified from [9]. *Abbreviations*: NET: neuroendocrine tumor; NEC: neuroendocrine carcinoma.

[a] 10HPF = number of mitoses for ten high power fields.

[b] Ki-67 index applies only to WHO and ENETS classification of GEP-NETs.