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Pancreatic neuroendocrine tumors: Challenges in an underestimated disease

A. Viúdez[a,*], A. De Jesus-Acosta[b], F.L. Carvalho[c], R. Vera[a], S. Martín-Algarra[d,1], N. Ramírez[e,**,1]

[a] Department of Medical Oncology, Complejo Hospitalario de Navarra, IdiSNA Navarra Institute for Health Research, Navarra Public Health System, Pamplona, Navarra, Spain
[b] Department of Medical Oncology, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Medical Institutions, Baltimore, Maryland, USA
[c] Department of Urology, Georgetown University Hospital, Washington DC, USA
[d] Department of Medical Oncology, University Clinic of Navarra, University of Navarra, IdiSNA Navarra Institute for Health Research, Pamplona, Spain
[e] Oncohematology Research Group, Navarrabiomed-Miguel Servet Foundation, IdiSNA Navarra Institute for Health Research, Navarra Public Health System, Pamplona, Navarra, Spain

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ABSTRACT

Pancreatic neuroendocrine tumours (PanNETs) are considered a relatively unusual oncologic entity. Due to its relative good prognosis, surgery remains the goal standard therapy not only in localized disease but also in the setting of locally or metastatic disease. Most of the patients are diagnosed in metastatic scenario, where multidisciplinary approach based on surgery, chemotherapies, liver-directed and/or molecular targeted therapies are commonly used. Owing to a deeper molecular knowledge of this disease, these targeted therapies are nowadays widely implemented, being the likely discovery of predictive biomarkers

* Corresponding author at: Medical Oncology Department, Complejo Hospitalario de Navarra, C/Irunlarrea 3, 31008 Pamplona, Navarra, Spain.
** Corresponding author at: Oncohematology Research Group, Navarrabiomed–Miguel Servet Foundation. C/Irunlarrea 3, 31008 Pamplona, Navarra, Spain.
E-mail addresses: antoniovb76@gmail.com, aviudez@outlook.es (A. Viúdez), nramireh@cfnavarra.es (N. Ramírez).
[1] Both as senior authors.

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that would allow its use in other settings. This review is focused on describing the different classifications, etiology, prognostic biomarkers and multidisciplinary approaches that are typically used in PanNET.

1. Introduction

Currently, the incidence of the pancreatic neuroendocrine tumours (PanNETs), so called since 2010, is considered low compared to other entities (about 0.4 cases per 100,000 inhabitants, according to SEER- National Cancer Institute Surveillance, Epidemiology, and End Results) (McKenna and Edil, 2014). On this basis, advances in diagnostic techniques and knowledge gathered in recent years have meant that currently they represent between 2–10% of all tumours diagnosed in the pancreas (Eriksson and Oberg, 2000; Metz and Jensen, 2008; Falconi et al., 2006a; Fraenkel et al., 2012) and about 7% of all neuroendocrine tumours, just below gastrointestinal carcinoid tumours (Lawrence et al., 2011; Yao et al., 2007; Oberg, 2010). This discrepancy in prevalence may be due to the absence of accurate records before 2000, because, until then, this disease was categorised within the "benign" or "uncertain" clinical course (Niederle et al., 2010). PanNETs affect males in a slightly higher proportion (McKenna and Edil, 2014) as well as Caucasians (Halfdanarson et al., 2008), presenting the peak incidence between the sixth and seventh decade of life (Hauso et al., 2008; García-Carbonero et al., 2010). However, PanNET presents at younger ages in patients diagnosed with multiple endocrine neoplasia type 1 (MEN-1) or in patients with symptoms of functioning PanNET (Shorter et al., 2002; Kent et al., 1981).

2. Etiologies and pathogenesis

The theory that supported that the PanNETs resulted from Langerhans cells can be now considered superseded by the findings of Vortmeyer et al. (Vortmeyer et al., 2004), who appreciated that the true genesis of this disease occurred in pluripotent stem cells of the pancreatic duct/acini, with a possible common origin between adenocarcinomas and PanNETs. Despite this phylogenetic confluence, there are differences between the molecular profile associated with PanNETs and the typical ductal adenocarcinomas. The most common mutations observed during tumorigenesis in pancreatic adenocarcinoma are hardly seen in PanNET (Jiao et al., 2011). In a similar vein, the most commonly observed mutations in PanNET, often acting on chromatin remodelling genes, are extremely rare in pancreatic adenocarcinomas (Jiao et al., 2011). The most frequent genetic alterations in PanNET occur in MEN1 (*Multiple Endocrine Neoplasia-1 Gene*), DAXX/ATRX (*Death-Domain Associated Protein/Mental Retardation Syndrome X-Linked Genes*) and the mTOR pathway (*Mammalian Target of Rapamycin*). The loss of the 2 alleles of the MEN-1 suppressor gene, which encodes the suppressor protein menin, occurs in about 25–30% of PanNETs (Corbo et al., 2010; Capelli et al., 2009), with mutation being the most frequent alteration (Jiao et al., 2011). In fact, germline MEN-1 mutations predispose to the development of multiple endocrine neoplasias, also known as the syndrome with the same name (MEN-type1).

Different chromosomal and genetic studies have suggested the existence of several genes with a potential impact on the development of PanNET, but, unfortunately, these findings have not been supported by the results of further functional and genetic analyses (Chung et al., 1998; Floridia et al., 2005; Hu et al., 2010). Recently, exomic-sequencing analysis performed on 68 samples of PanNET showed somatic inactivation mutations on MEN-1 in 44% of cases (Jiao et al., 2011). The same study showed the existence of mutations on DAXX/ATRX in 42.6% of cases. The high ratio of inactivating and missenses mutations observed on both genes resulted in assuming the role of both genes as tumour suppressors in PanNET. In addition, DAXX and ATRX are also involved in the chromatin remodelling of telomeres, and seem to play an important role in the process of telomere maintenance independently from telomerase. This is called alternative lengthening of telomeres (ALT) (Heaphy et al., 2011; de Wilde et al., 2012a; Marinoni et al., 2014; Dogeas et al., 2014) and it could explain the high prevalence of abnormal telomeres observed in samples of PanNET (Heaphy et al., 2011). The occurrence of such mutations and, therefore, the onset of telomeric abnormalities appear to be associated with the delayed development during PanNET tumorigenesis (de Wilde et al., 2012a), and more specifically to PanNET related to other neuroendocrine tumours (Dogeas et al., 2014). In those cases, The serine-threonine kinase mTOR pathway has a crucial role in tumour growth and proliferation (Missiaglia et al., 2010; Perren et al., 2000). Again, the work conducted by Jiao et al. (Jiao et al., 2011) quantified the existence of gene mutations belonging to this pathway, predominantly on PTEN (*phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase*), TSC-2 (*tuberous sclerosis gene-2*) and PIK3CA (*phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha*), in 14% of the cases, which could be important in the use of this pathway's inhibitors, like everolimus or temsirolimus.

3. Familiar syndromes associated with PanNETs

To date, four inherited syndromes associated with PanNET are known. The most common is the previously mentioned MEN-1 syndrome. These patients represent around 5% of PanNET and frequently patients with this syndrome develop multiple pancreatic tumours. Malignant potential appears to be mainly related to size, being tumours larger than 2 cm those with more aggressive behaviour (Metz and Jensen, 2008; Falconi et al., 2006a). The Von Hippel-Lindau (VHL) disease is an autosomal dominant syndrome that predisposes to a variety of cancers due to mutations in the VHL tumour suppressor gene located at 3p25, including PanNET. In contrast, VHL gene is uncommonly mutated in sporadic PanNET, where is usually inactivated by epigenetic mechanism (Meeker and Heaphy, 2014). In this context, generally PanNETs have good prognosis, although a small proportion of them develops in an aggressive disease (Hammel et al., 2000).

PanNETs can also be diagnosed in two other inherited syndromes, Neurofibromatosis type 1 and Tuberous Sclerosis. Neurofibromatosis type 1 (or Von Recklinghausen disease) is caused by a germinal mutation at 17q11.2. Theses patients are predisposed to develop somatostatinomas and, to a lesser extent, insulinomas (McClatchey, 2007). Tuberous sclerosis disease linkes to TSC1 (at 9q34) or TSC2 gene mutations (at 16p13.3). The association between both mutations and PanNET is extremely rare (Verhoef et al., 2015).

Although MEN4 syndrome, that is caused by a mutation in CDKN1B, has been recently described, its association with PanNETs is currently unknown (Pellegata, 2012; Thakker, 2014).