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Review Article

Digestive neuroendocrine neoplasms: A 2016 overview

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ABSTRACT

Digestive neuroendocrine neoplasms (DNENs) have an incidence of 2.39 per 100,000 inhabitants per year, and a prevalence of 35 cases per 100,000; the gap between these rates is to be referred to the relatively long survival that characterizes the majority of these tumors, which can be thus considered as chronic oncological diseases. Up to 80% of patients are stage IV since the first diagnosis, presenting a 5-yr overall survival rate of 35%–55% and a twice higher mortality than limited disease. DNENs express somatostatin receptors in more than 80% of cases, detected through immunohistochemistry or functional imaging tests (FITs). This feature identifies patients who may benefit from "cold" somatostatin analogs (SSAs) or peptide receptors radionuclide therapy, although SSAs are sometimes used also with a negative uptake at FITs. The therapeutic options have been recently increased after the identification of molecular pathways involved in DNENs pathogenesis, and the subsequent use of targeted therapies (i.e., Everolimus and Sunitinib) for these neoplasms.

This review offers an overview about pancreatic and small bowel NENs, critically underlining the issues that still need to be clarified and the future perspectives to be investigated.

1. Introduction

Digestive neuroendocrine neoplasms (DNENs) are usually considered as "rare" cancers, characterized by a gap between the low incidence and the prevalence. They are in fact frequently slowly growing, and behave as chronic oncological diseases with a relatively long survival [1–3]. Up to 80% of cases present as stage IV since diagnosis, with a 5-yr overall survival (OS) of 35%–55% and a mortality rate twice higher than patients without distant metastases [4–6]. As they are often occasionally found at the age of fifty or even earlier, it is easy to imagine the impact on quality of life that these conditions may cause.

DNENs express somatostatin receptors (SSTRs) in more than 80% of cases; this feature can be detected through immunohistochemistry or functional imaging tests (FITs), such as Somatostatin Receptor Scintigraphy (SRS), (also called Octreoscan®) or ^{68}Ga-DOTA-peptide Positron Emission Tomography (PET)/Computed Tomography (CT) (^{68}Ga-DOTA-PET/CT). These diagnostic tools have a pivotal role at diagnosis, completing disease staging and selecting cases eligible for peptide receptors radionuclide therapy (PRRT) or "cold" somatostatin analogs (SSAs); the latter treatment is however used also for patients with negative uptake at FIT [7,8]. After the identification of molecular pathways involved in DNENs pathogenesis (i.e., mTOR, VEGF signaling and TK inhibitors), the available options have been enriched by the introduction of targeted therapies (Everolimus, Sunitinib) [9–13]. However studies focusing on the mechanisms underlying the resistance to these drugs, the strategies to escape it and how to potentiate their efficacy, are still ongoing [14–17].

This review offers an overview about pancreatic (PNENs) and small bowel (SbNENs) NENs, critically underlining the issues that still need to be validated or optimized.

2. Epidemiology

The prevalence amounts for 35 cases per 100,000 inhabitants, and incidence has substantially increased over the past two decades, due to diagnostic techniques improvement [1,18]. In details, European age-adjusted rate raised from 13.3 to 21.3 per 100,000 person years. The estimated annual increase was of 5.1% in women and 2.1% in men, and it was more pronounced for tumors with intermediate aggressiveness.

Epidemiological data mostly derive from retrospective analysis, such as national registries. The only prospective study remains

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the paper by Niederle et al., collecting all newly diagnosed DNENs during one year in Austria according to the "World Health Organization" (WHO) classification and the "European Neuroendocrine Tumor Society" (ENETS) [19–22]. Among its results, overall incidence of tumors with benign, uncertain and malignant behavior was described as 1.15, 0.43 and 0.81 per 100,000 inhabitants, respectively. The tumor primary site was small bowel in 15% of cases, and pancreas in only 9%.

Up-to-date:

- Prevalence rate higher than incidence (chronic oncological disease)
- Increasing incidence over the last 20 years

Future perspectives:

- To promote European registries collecting NENs patients' information, with regular updating and data sharing, in order to produce papers with larger populations
- To develop prospective studies enrolling new NENs diagnosis in several countries, in order to define their incidence rate in Europe

3. Molecular pathogenesis

Over the last few years, there have been major advances in the understanding of the genetics and molecular pathogenesis of sporadic DNENs, identifying several pivotal pathways and providing new options in terms of therapy [23]. The mammalian target of rapamycin (mTOR) is an intracellular serine/threonine kinase regulating cell survival, proliferation and motility; its expression increases (without mutations) in PNENs and is correlated with a higher proliferation index (evaluated by ki67) and a worse prognosis. The antagonist of PI3K (PTEN) is instead mutated or lost in about 10%–29% of sporadic PNENs, correlated with a better clinical outcome. EGFR (ErbB-1), a member of the ErbB family of tyrosine kinase receptors, is also involved in the mTOR pathway, and its activation is a negative prognostic factor for patients, upregulating downstream effectors such as Akt and ERK. Src Family of Kinases (SFK) is implicated in EGFR transactivation, cell adhesion and spreading of tumoral cells [24–26].

Angiogenesis also seems to have a pivotal role in DNENs pathogenesis, as the vascular endothelial growth factor (VEGF) and its receptor (VEGFR) are expressed in these neoplasms and in the surrounding endothelia. Data evaluating their correlation with prognosis are controversial: some studies have proportionally related them to an aggressive tumor biology, others have paradoxically shown malignant forms as characterized by a lower VEGF expression. A possible explanation for this disparity might be that VEGF is somehow a marker of "well-differentiated" neoplasms; thus, when NENs are less differentiated and their rapid growth causes hypoxia, the hypoxia-inducible factors-1α (HIF-1α) pathway is activated, leading to an increase of endothelial proliferation. However, neoangiogenesis inhibition is the basis of a treatment choice for DNENs, using either tyrosine kinase inhibitors targeting the VEGFR and/or other related receptors [27,28].

Besides these pathways that have already provided a therapeutic approach, new mechanisms are being investigated. For example, mutations of the alpha-thalasemia/mental retardation syndrome, X-linked (ATRX), and death domain-associated protein (DAXX) genes have been identified in DNENs. Data suggest them to be correlated with a worse prognosis, based on telomerase activity and chromosomal instability; however larger studies are needed to validate these results [29,30].

Up-to-date:

- PI3K/Akt/mTOR pathway and angiogenesis markers are the protagonists of the currently available targeted therapies

Future perspectives:

- To better define the mechanisms underlining tumor escape from targeted therapies control, and defeat them by combining treatments acting on different pathway levels
- To identify new molecular pathways, opening new horizons in terms of targeted therapies

4. Clinical presentation

DNENs are defined as "functioning" (25%–35% of patients) when associated with a syndrome due to hypersecretion of hormones or amines. For SbNENs, a typical "carcinoid syndrome" may be present and really impair quality of life. It is characterized by release of serotonin determining diarrhea, cutaneous flushing (especially on the face and neck skin) and in 20% of cases a carcinoid heart disease (with cardiac valve disfunction) [31,32]. The conventional treatment is the use of SSAs, which have been proved to be very effective in symptoms control; however, as not responding patients may occur, telotristat etiprate has been recently proposed to treat severe cases [33–36]. This is an oral, systemically available drug, able to inhibit tryptophan hydroxylase, the rate limiting enzyme in the conversion of tryptophan to serotonin. The results of a Randomized Controlled Trial (RCT) (www.clinicaltrials.gov, NCT01677910) have been presented at the last European Cancer Congress (ECC; Vienna, September 2015); 135 patients with metastatic disease and uncontrolled carcinoid syndrome were randomly assigned to receive telotristat 250 mg ($n = 45$), telotristat 500 mg ($n = 45$), or placebo ($n = 45$). A significant clinical (improvement in diarrhea) and biochemical response was observed in the treatment arms; in details, both treatment groups met a reduced mean of bowel movements frequency than the placebo arm ($P < 0.001$), and the rate of cases with a durable response after the 12-week double-blind period was 44%, 42% and 20%, respectively. The therapy was continued at a dosage of 500 mg in an open-label regimen by 87% of patients.

In PNENs, syndrome can be due to release of: gastrin in "gastrinomas", vasoactive intestinal peptide in "VIPomas", insulin in "insulinomas" and somatostatin in "somatostatinomas". Clinical presentation is related to the different hormone released: gastrinoma diagnosis may follow the occurrence of diarrhea and gastric ulcers, not responding to high dose proton pump inhibitors; insulinoma patients may suffer from symptomatic hypoglycaemia, with sweating, confusion and even loss of consciousness [37].

"Non-functioning" tumors, instead, can be silent for years even though 75% of these patients already have an advanced disease at the beginning of their clinical history. Thus, diagnosis is often incidentally made at surgery or during radiological follow-up for other malignancies. They are for example found at imaging tests performed for non-specific symptoms such as nausea, vomiting, anaemia, or pain due to tumor local invasion, bowel obstruction or mesenteric ischaemia. In addition, they can also present with mass effect of the primary tumor or metastases on the adjacent structures (i.e., jaundice due to primary site in the pancreatic head).

Being "rare" diseases, with a genetic background still to be defined, screening programs are not available.