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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.

Table 1
World Health Organization (WHO) classification versions (1980, 2000, 2010).

WHO 1980	WHO 2000	WHO 2010
I. Carcinoid	1. Well-differentiated endocrine tumor (WDET) 2. Well-differentiated endocrine carcinoma (WDEC) 3. Poorly-differentiated endocrine carcinoma/small-cell carcinoma (PDEC)	1. NET G1 (carcinoid) 2. NET G2 3. NEC G3 large-cell or small-cell type
II. Mucocarcinoid	4. Mixed exocrine-endocrine carcinoma (MEEC)	4. Mixed adenoneuroendocrine carcinoma (MANEC)
III. Mixed forms carcinoid-adenocarcinoma		
IV. Pseudotumor lesions	5. Tumor-like lesions (TLL)	5. Hyperplastic and preneoplastic lesions

Up-to-date:

- DNENs may be an incidental diagnosis in case of "non functioning" tumors

Future perspectives:

- To identify biomarkers, effective in early diagnosing non-functioning DNENs, allowing early treatments and influencing prognosis

5. Prognostic factors and classifications

Due to their biological and clinical heterogeneity, DNENs may show different prognosis; in fact, some tumors have a very malignant behavior, whereas in other patients disease may be stable for a long time even without any treatment. Several prognostic factors have been identified until now.Tumor primary site has been proved to affect OS by different papers, with pancreas showing a worse outcome than small bowel (5-yr survival rates: 62% vs. 89.9%, respectively) [38,39].

Ki67 indicates neoplastic replicative index as the rate (expressed in percentage) of tumoral cells being in replicative phase, identified by positivity at a specific immunohistochemical staining. It represents the major, independent risk factor for disease progression (DP) in DNENs, with a hazard ratio (HR) of 1.02 for each increasing unit ($P < 0.001$) [6]. The G Grading classification has been proposed by the ENETS, identifying 3 categories of patients: G1 when ki67 is $\leq$2%, G2 when 3%–20%, and G3 if >20% [20,21]. Although several papers have shown how the G Grading affects clinical outcome and response to therapy, the cut-off values are currently debated, in order to distinguish homogeneous groups. For example, G3 cases are affected by more active and aggressive neoplasms than G1/G2, but this group is represented by the major range of ki67 (from 21% to 100%); furthermore, the 55% cut-off has been proved to be associated with a different tumor response to chemotherapy (CHT). G1–G2 definition is being discussed as well, and an alternative value of 5% instead of 2% has been applied in retrospective series, testing its prognostic meaning in DNENs [5,6,38–41].

In parallel, the WHO classification has been introduced in 1980, revised in 2000 and then in 2010 (Table 1). This last version adopted the term "neuroendocrine" instead of "endocrine", and beyond the histological differentiation it considered also G Grading to describe the tumoral subgroups [20]. For what concerns the third category (NEC G3), a subclassification distinguishing "well" vs. "poorly-differentiated" cases is currently discussed (NET G3 vs. NEC G3), as data in literature prove them to represent different populations; however larger series and prospective studies are needed to validate this suggestion [42].

For what concerns the disease staging, in 2006–2007 the ENETS TNM system was published, with T indicating tumor size and regional extent, N indicating the presence of lymph nodal involvement and M representing the distant metastases [21,22].

Table 2
TNM staging systems for pancreatic neuroendocrine neoplasms according to the American Joint Committee on Cancer (AJCC) and the European Neuroendocrine Tumor Society (ENETS).

AJCC		ENETS
T1	Tumors limited to the pancreas, <2 cm	Tumors limited to the pancreas, <2 cm
T2	Tumor limited to the pancreas, >2 cm	Tumor limited to the pancreas, 2–4 cm
T3	Tumor extended beyond the pancreas, but not involving celiac axis or superior mesentery artery	Tumor extended beyond the pancreas, or invading duodenum or common bile duct
T4	Tumor involving celiac axis or superior mesentery artery	Tumor invading adjacent structures
N0	No regional lymph nodes metastases	No regional lymph nodes metastases
N1	Presence of regional lymph nodes metastases	Presence of regional lymph nodes metastases
M0	No distant metastases	No distant metastases
M1	Presence of distant metastases	Presence of distant metastases

AJCC		ENETS	
IA	T1 N0 M0	I	T1 N0 M0
IB	T2 N0 M0	IIA	T2 N0 M0
IIA	T3 N0 M0	IIB	T3 N0 M0
IIB	T1-3 N1 M0	IIIA	T4 N0 M0
III	T4 N0-1 M0	IIIB	Any T, N1 M0
IV	Any T, Any N, M1	IV	Any T, Any N, M1

The "American Joint Committee on Cancer" (AJCC) has proposed another TNM in 2010; Table 2 directly compares the AJCC and the ENETS systems [43].

Stage IV (any T, any N, M1) NENs have a 5-yr OS of 35%–55% vs. 70%–100% of lower stages, and a two-fold higher mortality rate [4–6]; however, this group does not include a homogeneous series of patients. In details, a recent paper has shown how the different metastatic pattern is an independent prognostic factor from Ki67, with poorer OS and progression-free survival (PFS) rates for patients with extra-abdominal lesions than cases with only bilobar or unilobar secondaries; median PFS was 6 months, 19 months and 27 months, respectively ($P = 0.0002$) [6].The presence of lymph nodal disease has also been proved to represent a risk factor for PNENs, with a HR of 2.75 for patients with a lymph nodal ratio >0.20 ($P < 0.02$) [44]. For SbNENs, the role of this parameter still needs to be clarified [45].

Up-to-date:

- Ki67 and the disease staging have been proved to be the major prognostic factors for DNENs, followed by the tumor primary site
- The WHO 2010 and the ENETS TNM staging system are the mostly used classifications in Europe; they have been validated only by retrospective studies

Future perspectives:

- To improve the current TNM, WHO and G Grading classifications by prospective studies, focusing on the definition of stage IV subgroups, and the distinction between NET G3 and NEC G3
- To associate all the significant factors in order to define "risk scores", useful to early describe the prognosis of each patient

6. Diagnosis

The sure diagnosis is based on histologic evaluation with immunohistochemistry, by identifying: neuroendocrine cells expressing chromogranin A (CgA) and synaptophysin, tumoral morphology (the grade of differentiation: well, moderately, poorly), and ki67 expression. Biopsy can be obtained through endoscopic procedures (esofagogastroduodenoscopy, colonoscopy, endoscopical ultrasound), liver biopsy on metastases or surgery [46,47]. Together with the pathological definition, tumor staging is also needed to assess the disease extent; this evaluation can be performed by morphological tests (contrast-enhanced CT scan and Magnetic Resonance Imaging; MRI) and FITs (SRS and ^{68}Ga-DOTA-PET/CT) [9,10].

FITs identify lesions expressing SSTRs, and thus patients eligible for somatostatin-based therapies (SSAs or PRRT) [9,10,48,49]. ^{68}Ga-DOTA-PET/CT has a higher accuracy both in detecting intra- and extra-abdominal lesions. In fact, it is CT-based and able to gather a quantitative measure of signal intensity through the Standardized Uptake Value (SUVmax) [50].

Besides these tests, others are being studied to understand what is their real usefulness if adopted for DNENs diagnosis. The diffusion-weighted MRI is proposed in metastatic patients to use the apparent diffusion coefficient (ADC) calculated during the exam as a potential marker of the histologic grade of PNENs, and as a predictor of response to selective internal radiotherapy (SIRT) [51,52]. The 18F-fluorodeoxyglucose PET/CT 18F-FDG-PET/CT is a FIT documenting the metabolic activity of tumoral lesions and, as many NENs present a low ki67, it has been reserved only to selected cases; in fact the positivity at 18F-FDG-PET/CT seems associated with low differentiated and high proliferating neoplasms [53,54]. In details, Bahri et al. [55] prospectively enrolled in a 3-year period 38 patients with metastatic DNENs, followed-up for 55.2 ± 37.9 months. They demonstrated a positive 18F-FDG-PET/CT with a SUV ratio of at least 2.5 to be a negative prognostic factor, with a 4-year survival rate of 0%; furthermore, this exam was advised also for patients expressing SSTRs, as among them PFS and OS rates were significantly shorter when the 18F-FDG-PET/CT was positive ($P < 0.0001$). Data available in literature are however controversial, as Partelli et al. [56] have shown, in 49 PNENs, no significant impact on clinical management with the association of 18F-FDG-PET/CT and ^{68}Ga-DOTA-PET/CT.

Up-to-date:

- Diagnosis is based on histological evaluation with calculation of ki67, and disease staging by morphological and functional exams
- Functional imaging tests are also needed to identify patients who may benefit from somatostatin-based treatments

Future perspectives:

- To validate in new prospective studies the role of diffusion-weighted MRI and 18F-FDG-PET/CT in DNENs, evaluating what is the adjunctive impact of their use in patients management, and to which cases they should be reserved

7. Therapy

Being characterized by a relatively long OS, multiple sequential therapies are adopted in DNENs although the best sequence for these patients has never been defined so far. The surgical treatment with radical intent is the option to prefer [57], but no data are available about adjuvant treatments.

Another open issue is the management of non metastatic pancreatic nodules with a size <2 cm, as studies are needed to define the best approach between radical surgery or only follow-up according to the potential indolent behaviour of these lesions [58]. The European trial entitled "Follow-up Protocol of Sub-2cm Pancreatic NETs", is quite aimed to compare these two options, and has been recently proposed at the last annual ENETS Conference (Barcelona, March 2016).

In some cases (especially with functioning tumors) when a complete resection is not possible, surgery is performed in order to reduce symptoms. This approach can be based combining surgery on primary and secondary tumors with locoregional treatments (i.e., trans-arterial liver embolization, TAE; trans-arterial chemoembolization, TACE; radiofrequency ablation, RFA) [9,10]. Data about long-term prognosis after this approach are however scanty. The opportunity to resect the primary site in advanced tumors has been widely discussed; two systematic reviews of the literature suggested a possible benefit of this approach in terms of OS for both PNENs and SbNENs but, as no RCTs were available, metanalyses could not be performed and a strong conclusion not pointed out [59,60]. Liver transplant is reserved to very well selected patients with a neoplasm limited to the liver, but data derive from small cohorts [61,62].

Another experimental approach to metastatic disease is SIRT, based on the intra-arterial deliver of Yttrium-90 microspheres to the lesions. Although results seem appealing, they derive from retrospective series, and a recent study comparing this technique to TAE and TACE over a 10-year period did not show any advantage in terms of time to DP [63].

For what concerns medical treatments, especially if G1 and G2, the first-line therapy is frequently SSAs, considering their efficacy and good safety profile. Binding to the receptors on tumoral cells surface, they are mostly prescribed when tumors express SSTRs, but sometimes also to patients with a negative uptake at FIT. Beyond their effect on symptoms due to the functional syndromes, they are also able to control tumor proliferation, as shown by two RCTs. The PROMID study has described, in 42 metastatic midgut patients treated with octreotide LAR 30 mg, a median PFS of 14.3 months vs. 6 months of the 43 cases in the placebo group. The CLARINET trial has shown, in 101 DNEN patients using lanreotide 120 mg, a 24-month PFS of 65.1% vs. 33.0% of the 103 receiving no therapy [64–67].

In clinical practice, in case of DP during this treatment, a higher dosage or a shorter interval of administration is a possible strategy, but it is not "evidence-based". A new RCT (CLARINET FORTE, NCT02651987) is currently recruiting DNEN patients to be treated with lanreotide 120 mg every 2 weeks, after DP observed during lanreotide every 4 weeks.

Besides these formulations, pasireotide is a novel SSA still under investigation. "In vivo" data derive from an open-label, phase II study enrolling 29 naïve patients with metastatic NET G1 and G2 disease showed: a PFS of 11 months, a 30-month OS rate of 70%, partial response (PR) and stable disease (SD) in 1 and 17 cases, respectively. Major predictors of response were low hepatic tumor burden, normal baseline CgA and SSTR5 expression. In fact, binding affinity for SSTR2 and SSTR5 respectively are: 0.4–2.1 and 5.6–32 for octreotide; 0.5–1.8 and 0.6–14 for lanreotide; 1 and 0.16 for pasireotide. However, the high incidence of hyperglycemia (79%) due to pasireotide is against its use as a first-line approach [68,69].

PRRT acts with the same molecular mechanism, but somatostatin analog is radiolabeled with Y90 or Lu177, performing an "in loco" radiotherapy; this well tolerated treatment is able to inhibit tumor growth in up to 50%–70% of DNENs [70,71]. Results of the first Phase III multicentric RCT comparing Lutathera® vs. Octreotide in patients with inoperable, progressive, SSTR-positive G1–G2 SbNENs (NETTER-1 trial) have been presented at the last ECC (Vienna, September 2015) (www.clinicaltrials.gov, NCT01578239). They have showed how, in 230 patients enrolled, the median PFS was not reached in the PRRT-treated group vs. 8.4 months obtained by SSA (HR: 0.21, $P < 0.0001$). These data support the benefit of this therapy in metastatic SbNENs with a good safety profile, and will pave the way to its official registration [72].

Another relevant option for DNENs is represented by targeted therapies. In the RADIANT-3 trial, a phase III placebo-controlled study enrolling advanced PNENs, Everolimus (RAD001, Afinitor®, Novartis Oncology) offered a significant prolongation in median PFS vs. placebo (11 and 4.6 months; 207 and 203 patients; respectively). This result led to its approval by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of locally advanced, metastatic or unresectable PNENs [11,13]. The RADIANT-4 RCT has been recently published evaluating the efficacy of Everolimus 10 mg/die compared to placebo in progressive, well-differentiated, non-functioning lung and non-pancreatic DNENs [73]. This study has proved a significantly higher PFS in the 205 patients enrolled in the treatment arm than in the 97 receiving placebo (11 vs. 3.9 months, respectively; HR: 0.48; $P < 0.001$). Disease stabilization was reached in 81% of the treated cases vs. 64% of the placebo arm; PR was observed in 4 and 1 cases, respectively. Everolimus benefit was significant also in terms of mortality rate, with a 36% reduction in the risk of death (HR: 0.64; $P = 0.037$).

Instead, results from COOPERATE-2 phase II study have been presented at the ENETS 2015 Conference, proving a non significant yield in terms of PFS adding Pasireotide to Everolimus in advanced G1/G2 progressing PNENs [74].

Beyond its efficacy, resistance to treatment with Everolimus may occur, due to tumoral escape routes activating the upstream PI3K/Akt pathway. Possible strategies to solve this problem might be the association of other drugs, acting on the same pathway (vertical inhibition) or on another one (horizontal inhibition), but these mechanisms still need to be explored [14–17,23].

Sunitinib (Sutent®, Pfizer) is another targeted therapy, with antiangiogenetic action against VEGFR, PDGFR, c-KIT, Flt-3 and RET. Trials published on PNENs have shown its ability to determine a PFS of 10.2 months vs. 5.4 with placebo, together with improvement of OS rate [12,13]. Pazopanib also (Votrient®, Glaxo Group, London, UK) has an antiangiogenetic activity; it has been investigated as a monotherapy in phase II studies enrolling metastatic DNENs pretreated with other therapies (including targeted drugs) [75,76]. A recent trial has also evaluated its efficacy in controlling tumor proliferation in 52 patients affected by advanced well-differentiated NETs treated with pazopanib and octreotide, reporting an objective response rate of 21.9% in PNETs, and null response in carcinoid patients [77]. Bevacizumab is another antiangiogenetic option; in the American Society of Clinical Oncology (ASCO) 2015 Conference, results from a phase III prospective trial (www.clinicaltrials.gov, NCT00569127) were presented. The study included 402 advanced G1/G2 progressive carcinoid patients, randomized to be treated with depot octreotide plus interferon alpha-2b (IFN), or with depot octreotide plus bevacizumab (BEV). No significant difference in PFS was observed among the two arms, suggesting that BEV and IFN have a similar antitumor activity in this population [78].

Treatment of G3 NENs is not well defined, as most of the RCTs so far published include G1–G2 patients. CHT is widely adopted, especially for poorly-differentiated neoplasms, but data comparing the different regimens and deriving from large series are still lacking. There are only few trials published, and mostly not randomized, enrolling well-differentiated cases and focusing on streptozotocin, temozolomide and capecitabin [79–81]. Results are controversial, as previous studies have suggested patients to benefit from CHT (especially with Ki67 >55%) in terms of objective response, although changes in OS rates are not impressive [47]; on the other side, the German experience proposes to use this approach also as a first-line choice in locally advanced G1–G2 PNENs, with an unexpected worse outcome with ki67 <15% [82].

If patients with well-differentiated G3 tumors might benefit from Everolimus is unknown, as the previous RCTs on this drug excluded these patients from recruitment. The ongoing EVINEC trial (www.clinicaltrials.gov, NCT02113800) is enrolling cases with G3 NENs to receive Everolimus as a second-line treatment after a first-line platinum-based regimen; endpoints will be PFS, OS and safety/tolerability.

Up-to-date:

- SSAs are safe and effective as a first-line approach for well differentiated-DNENs
- Targeted therapies (Everolimus and Sunitinib) have been approved for advanced G1–G2 PNENs, and proved to be effective also in the other DNENs
- PRRTs has been proved to be indicated for advanced midgut NENs

Future perspectives:

- To identify categories of patients at risk for recurrence after radical surgery, and then define the therapeutic option to adopt (CHT? SSAs?)
- To define the management of small non metastatic PNENs (surgery vs. follow-up)
- To develop RCTs aimed to directly compare the efficacy of targeted therapies and PRRT in advanced well-differentiated DNENs
- To evaluate in RCTs the efficacy of chemotherapies, comparing the available regimens and their use in different lines approach

8. Tumor response assessment

Tumor response (SD or down-staging vs. PD) is usually assessed by CT scan and MRI according to the RECIST criteria [9,10,83]. However, the validity of these criteria is under revision, as after the introduction of targeted therapies and PRRT the feeling of clinicians is that morphological exams might fail to offer all the needed information. In clinical practice, FITs or diffusion-weighted MRI are adopted to respectively evaluate change in metabolic activity/SSTRs expression, or vascular pattern; however no prospective studies supporting this strategy have ever been performed, and this approach is based on medical experts opinions. The open debate is focusing on the cost/benefit ratio of follow-up programs, as for some patients too many procedures are repeated without any clear advantage, while for others conventional imaging tests are not enough. The correct timing to repeat each of them has not been defined yet, not even in the current Guidelines where the suggestion to repeat FITs every 12–24 months is present, but for which patients and with which time frame is not indicated [9,10,84].

Circulating CgA is a specific biomarker for DNENs. Several cut-off values have been proposed to evaluate its accuracy in detecting DP, but studies are mostly retrospective and based on small case series [85–87].

Up-to-date:

- CT scan and MRI are the tests usually adopted to follow DNENs up, and the RECIST criteria are the tools available to evaluate response to treatments and disease status

Future perspectives:

- To evaluate the clinical usefulness of FITs, including 18F-FDG-PET/CT, and diffusion-weighted MRI during DNENs follow-up, especially in patients facing targeted therapies or PRRT
- To define the correct timing to repeat these imaging tests after DNENs diagnosis
- To assess the clinical usefulness of circulating CgA in prospective trials, and to identify alternative biomarkers for these patients

9. Conclusions

DNENs can be considered as chronic oncological diseases, in which patients face several sequential treatments. Moreover, being "rare" neoplasms, it is hard to develop RCTs and most of the studies published focus on PFS to evaluate response to therapies. According to DNENs heterogeneity in terms of prognosis, a specific tailored treatment is needed for each patient. Current Guidelines offer useful tools for clinicians, but future perspectives should focus on several critical issues, such as to reevaluate available classifications, to optimize DNENs follow-up (without useless diagnostic tests for low risk patients, and with a more complete program for high risk cases), and to promote new trials directly comparing targeted therapies with PRRT.

Conflict of interest

None declared.

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