Review Article

Therapy for metastatic pancreatic neuroendocrine tumors

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Background: Pancreatic neuroendocrine tumors (pNETs) are frequently malignant (50-80%, except for insulinoma) and may show an aggressive course with metastases to the liver as well as more distant sites. These heterogeneous neoplasms include functioning tumors, which secrete a variety of peptide hormones, and non-functioning tumors (up to 90% of pNETs), which often show metastases at the time of diagnosis.

Methods: A PubMed search was performed for English-language publications from 1995 through December 2012. Reference lists from studies selected were manually searched to identify further relevant reports. Manuscripts comparing different therapeutic options and advances for metastatic pNETs were selected.

Results: The therapeutic options for metastatic pNETs are expanding and include surgery, which remains the only curative approach, liver-directed therapies, and medical therapy. In selected cases also liver transplantation (OLT) may be considered. The option of OLT for metastatic disease is unique to neuroendocrine tumors. Recently, novel promising targeted therapies have been proposed for progressive well-differentiated pNETs.

Conclusions: The best therapeutic approach for pNETs is still matter of debating. However, since pNETs often show a more indolent behavior compared to other malignancies, the preservation of the quality of life of the patient and the personalization of the therapy according to tumor's and patient's features are mandatory.

Keywords: Pancreatic neuroendocrine tumors (pNETs); duodenocephalopancreasectomy; liver metastases; liver-directed therapies; somatostatin analogues; liver transplantation

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Introduction

Pancreatic neuroendocrine tumors (pNETs) are fairly rare neoplasms, which constitute approximately 2% of all pancreatic tumors with a recent increasing incidence (1). Their clinical incidence is reported to be of 1-5 new cases/100,000 population per year with a prevalence of 10/100,000 population (2). These heterogeneous neoplasms include functioning tumors, which secrete a variety of peptide hormones, and non-functioning tumors, which often show metastases, mainly liver metastases, at the time of diagnosis; up to 90% of pNETs are non-functioning (3) and frequently secrete pancreatic polypeptide, chromogranin A (CgA), neuron-specific enolase, human chorionic gonadotropin subunits, calcitonin, neurotensin or other peptides (4). Functioning pNETs are associated with specific clinical syndromes, which include insulinoma (48%), gastrinoma (24%), VIPoma (13%), glucagonoma (12%), somatostatinoma (1%), and rarely GRHoma, ACTHoma, carcinoid syndrome and hypercalcemia due to PTHrp-oma (4). As regards the clinical aspect, functioning tumors determine the various clinical syndromes due to the secretion of specific hormones (i.e., insulinoma, gastrinoma, glucagonoma, VIPoma, and somatostatinoma), whereas patients with non-functioning tumors often experience symptoms related to the mass-effect due to metastases,

mainly at the liver, such as pain, anorexia, and weight loss (5).

The majority of pNETs occur sporadically, but these tumors may also be related to some specific inherited syndromes, including multiple endocrine neoplasia (MEN) type-1, von Hippel-Lindau disease, and tuberous sclerosis (6). PNETs associated with such syndromes have different prognosis and clinical course when compared with sporadic tumors and receive different therapeutic approaches. Moreover, these tumors may represent subgroups particularly responsive to novel therapies targeting the underlying genetic defect or pathway (7).

As concerns diagnostic pathway, imaging techniques [i.e., ultrasound or contrast-enhanced computed tomography (CT) or magnetic resonance (MRI)] are necessary to detect both the primary tumor and metastases. Somatostatin receptor scintigraphy (SRS) is suggested to detect metastases, including extrahepatic disease, although positron emission tomographic (PET) using 68 Ga appears to be more sensitive, particularly in case of small lesions. Ultrasound endoscopy (EUS) is recommended to detect small pancreatic tumors and to achieve a hystogical diagnosis by means of fine needle aspiration. Laboratory tests, including CgA, Pancreatic Polypeptide and specific hormones according to clinical presentation should be performed in all patients at the diagnosis and during follow-up (8,9). CgA has been described to be the best marker in patients with NETs in both sporadic and MEN1-related forms, and the highest CgA values usually occur in patients with metastatic disease (10).

Prognostic factors include histological grading, tumor differentiation, and the tumor staging. According to the recent World Health Organization (WHO) 2010 classification, three classes of tumors are identified (G1, G2, and G3): well-differentiated NETs can be classified as G1 tumors, when they express <2 mitoses/10 HPF and ≤2% Ki-67 index; as G2 tumors, when they express 2-20 mitoses/10 HPF and 3-20% Ki-67, whereas neuroendocrine carcinomas (NECs) usually belong to G3 category, with >20 mitoses/10 HPF and >20% Ki-67 index (11). However, the presence of metastases, mainly liver metastases, represents one of the most important strongly negative prognostic factor (12). In European and US referral centers, patients with pNETs often present with distant metastases at initial diagnosis (12). The occurrence of liver metastases is related to tumor extent (T-stage), differentiation, and grading (G1-G3); approximately 50% of poorly differentiated neuroendocrine carcinomas (NEC G3) are metastatic at initial diagnosis versus only 21% and 30% of well-differentiated and moderately differentiated neuroendocrine tumors (NET G1 and G2), respectively (12). The site of the primary tumor also has prognostic significance, since pNETs are usually characterized by a worse clinical course when compared with gastrointestinal tumors, with a 5-year survival rate of 30-60% versus a rate of 60-90% for carcinoids (13,14).

At present, a variety of therapeutic options exist for metastatic pNETs, including surgery, loco-regional therapies, chemotherapy, biotherapy with somatostatin analogues (SSAs) and interferon (IFN) and, more recently, the novel molecular targeted therapies and the systemic peptide receptor radionuclide therapy. Also liver transplantation (OLT) may be evaluated in highly selected patients (12).

Our review summarizes the available data on therapeutic approaches for advanced pNETs, comparing different options and highlighting recent advances.

Materials and methods

A literature search was conducted to identify all relevant papers dealing with different therapeutic approaches in patients with advanced pNETs. PubMed was used to search for all articles published from 1995 until December 2012 using the following keywords: pancreatic neuroendocrine tumors (pNETs), duodenocephalopancreasectomy, liver metastases, liver-directed therapies, somatostatin analogues, targeted therapy and liver transplantation. Reference lists from studies selected by the electronic search were manually searched to identify further relevant reports. Reference lists from all available review articles, primary studies and proceedings of major meetings were also considered. Articles published as abstracts were included, whereas non-English language papers were excluded.

Results

The optimal management of patients with advanced pNETs is still matter of debating. Therapeutic approaches for management of metastatic disease include surgical, medical, radiological and nuclear medicine strategies. More recently, novel molecular targeted drugs have been introduced and approved by The Food and Drug Administration (FDA) as therapeutic options in patients with progressive well- or moderately differentiated, unresectable localized pNETs (15,16). In selected patients, OLT may be evaluated (12).

Surgical resection of the primary tumor and of the metastases remains, when possible, the only curative treatment in patients with all types of NETs. However, poorly differentiated tumors are almost exclusively managed with chemotherapy, since surgery or other liver directed therapies are often not indicated. Multidisciplinary care and multimodality treatments remain the cornerstone of management of pNET patients. Furthermore, both the preservation of a satisfactory quality of life (QoL) for the patient and the personalization of the therapeutic approach according to the tumor's features and prognostic factors should represent the essential aspects of therapy for pNETs (17).

Management prior to treatment

In patients with pNETs, assessment of the tumor extent and location as well as evaluation of prognostic factors and patient's performance status and comorbidities are required to define the proper treatment (18-20). The evaluation of the tumor extent and the identification of the exact site of the primary and metastatic lesions are necessary to decide whether a curative surgical approach is possible. Standard abdominal ultrasound, EUS, CT scan, and MRI study are used to assess tumor extent and the possible location of the primary lesion (18,19). SRS should also be routinely performed, mainly to evaluate the extent of metastatic disease (18,19,21) and, more recently, there has been an increasing use of PET scanning based on 68Ga-radiolabeled SSAs (22,23). The use of SRS or Ga68-based PET is aimed both at identifying distant metastases, particularly bone metastases which are a poor prognostic factor and a contraindication to surgery (13), and to detect SSA's receptors prior to medical therapy or radiolabeled SSAs.

Since well differentiated pNETs show a different behavior from poorly differentiated pNETs with a consequent different therapeutic approach, a complete histological assessment of the tumor by means of biopsy, including the detection of mitotic ki-67 index, is needed prior to treatment (6,24).

The management of patients with neuroendocrine tumors includes a proper assessment of patient's characteristics, performance status and prognostic factors in order to tailor the therapeutic approach to every single patient. Furthermore, different prognostic factors, particularly in case of advanced pNETs, should be assessed in all patients both prior to and throughout the treatment.

Therapeutic approach

Surgery remains the only curative approach for neuroendocrine tumors whenever possible; in case of poorly differentiated tumors, surgery as well as other liver-directed therapies such as embolization are almost never applicable, and these patients are mainly managed with chemotherapy.

In case of functioning well-differentiated neuroendocrine tumors, it is important to control the hormone hypersecretion, which determines symptoms, usually by the administration of SSAs (18,19). In the Zollinger-Ellison syndrome, the milestone of therapy is the administration of high-dose proton pump inhibitors, whereas the hypoglycemia typical of insulinoma can be controlled by frequent small feedings and the use of diazoxide (19,25).

Besides surgery, a variety of therapeutic options exist for metastatic neuroendocrine disease: i.e., loco-regional therapies, medical therapy including chemotherapy, biotherapy with SSAs and IFN, and, more recently, the novel molecular targeted therapies and the systemic peptide receptor radionuclide therapy. Furthermore, in highly selected patients OLT might be considered (12). Different therapeutic options for advanced pNETs are summarized in *Table 1*.

Surgery

Surgery remains the only curative treatment for patients with pNETs and it is associated with an increased survival (26). Surgical resection is usually performed either when all the tumor can be completely removed or when it is possible to resect at least >90% of the neoplastic tissue (20). Otherwise, according to available data, debulking surgery is not usually performed because a significant improvement in survival has not been reported (8,27). Moreover, in case of pNETs with unresectable liver metastases, the surgical resection of the primary tumor is not routinely recommended (28).

According to a recent study, patients with pNETs, although considered unresectable because of vascular involvement, should undergo surgical exploration. In this study, in 91% of the 46 patients, firstly considered unsuitable for surgery, pNETs could be surgically removed, with a 30% remaining disease-free at 5-year follow up (29).

The tumor size is another key-factor to be considered in the therapeutic decision. Most of neoplasms <2 cm are likely benign or intermediate-risk lesions and only 6% of non-functioning pancreatic NETs <2 cm are malignant when

Table 1 Summarize of different therapeutic approaches in advanced pancreatic neuroendocrine tumors (pNETs), according to ENETS guidelines (12)

Surgery of the primary
• Curative when all the tumor can be completely removed or when it is possible to resect at least >90% of the neoplastic tissue
• Preferable when tumors >2 cm
• In case of metastatic tumor, if the tumor is >2 cm, and in case of a yearly increased size >0.5 cm in MEN1 patients
Somatostatin analogues
• Always in pNETs characterized by a slowly proliferative index (G1)
• Data on the efficacy of SSAs in NET G2 are still lacking
• Not recommended in metastatic non-functioning pNETs G3
• Somatostatin receptor scintigraphy and/or Octreotide test are needed prior to start the therapy
α-interferon
• Applicable in G1 tumors, slowly progressive pNETs and/or somatostatin receptors-negative tumors
• Usually administered in combination with SSAs
Chemotherapy
• Recommended in advanced inoperable well-differentiated (G1, G2) pNETs in case of failure of other treatments (i.e. biotherapy or targeted therapy), rapid tumor growth, poorly controlled symptoms, or poor prognosis, and in NEC G3 of any site
• Streptozotocin-based chemotherapies are still the gold standard, although dacarbazin, temozolomide or oxaliplatin regimens have been shown to be effective
• In NEC G3 chemotherapy is almost exclusively based on platinum regimen
Targeted therapies (i.e., everolimus and sunitinib)
• Recommended in patients with advanced pNETs after the failure of systemic chemotherapy, whereas its administration as first-line therapy should be reserved for selected cases
• In the United States, everolimus might be used as a possible first line therapy for unresectable well-differentiated pNETs
Radiolabeled somatostatin analogues
• Treatment option for unresectable or metastatic pNETs
• Somatostatin receptor scintigraphy is required prior to start the therapy
Liver directed therapies
• Ablation methods are generally reserved for unresectable metastases measuring less than 5-7 cm in diameter
• Hepatic arterial embolization (TAE) or chemoembolization (TACE) can be applied in the treatment of liver metastases from all types of NET G1/G2
Liver transplantation
• Selected cases

incidentally discovered (30). In selected cases, when tumors are <2 cm and incidentally discovered, a non-operative approach could be advocated. An intensive 3-month follow-up for the first year and the 6 months up to 3 years is suggested for these patients (8).

In patients with MEN-1, surgical resection of pNETs is generally recommended in case of metastatic tumor, if the tumor is >2 cm, and in case of a yearly increased size >0.5 cm (31). On the contrary, pNETs <2 cm seem to have a more indolent behavior and their appropriate management is still matter of debating (8).

Medical therapy

In case of advanced pNETs, refractory to surgical approach, systemic medical therapy is still considered to be the only available option (17).

Somatostatin analogues

SSAs have been suggested to be effective not only to control symptoms due to hormonal secretion, but also as anti-tumor growth agents in pNETs, although their exact mechanisms

are still far to be clearly understood (32).

The rationale of the use of SSAs in pNETs as well as in other NETs, is that functioning and non-functioning pNETs express at least one of the five subtypes of somatostatin receptors (SSTRs 1-5), which can be detected by molecular biological techniques or SRS, in the majority of patients. Various SSAs exhibit specific affinity for different SSTRs: in details, octreotide and lanreotide bind mainly to SSTR2, and much less to SSTR5. The more recent analogue pasireotide is considered as a 'pan-receptor' SSA, having a high affinity for SSTR1, SSTR2, SSTR3 and SSTR5 subtypes (33).

Moreover, an octreotide test may be performed prior to start medical therapy with SSAs to identify the subgroup of patients most likely to be responsive to chronic administration of SSAs (34).

According to available data, almost all functioning tumors benefit from SSAs. Several studies have supported the use of SSAs to control tumor growth in all types of NETs (35-38), but, to date, only one randomized, placebo-controlled phase III trial has been completed, which showed that octreotide LAR was effective in both functioning and non-functioning intestinal tumors, and patients receiving octreotide LAR for at least 6 months experienced a 66.7% reduction in the risk of disease progression compared with patients taking a placebo (39). However, significant results have been achieved only in a specific setting of patients [low liver load (≤10%) and resected primary tumors], thereby further studies are needed to determine whether these data can also be applied to patients with a large tumor load, with high Ki-67 and in case of pNETs. A similar multinational trial is also being carried out in patients with pNETs using Lanreotide-Autogel (120 mg/month) [CLARINET (Controlled study of Lanreotide Antiproliferative Response in NETs) study], but the results are not yet reported (32). In details, CLARINET is a 96-week, multinational study being conducted in patients with well or moderately differentiated non-functioning gastro-entero-pancreatic-NETs and a Ki67 <10%. Patients are stratified according to prior tumor progression status and presence/absence of previous therapies, and treated with lanreotide Autogel 120 mg or placebo. The primary endpoint is time to either disease progression or death, whereas secondary endpoints of the study include proportion of patients alive and without tumor progression at 48 and 96 weeks, time to progression, overall survival, safety, QoL, plasma CgA levels, tumor markers, and pharmacokinetic parameters.

Although there is an increasing evidence of the anti-tumor growth effect of SSAs in pNETs, <10% of patients experience an objective tumor response with a decrease in pNET tumor size following SSA therapy; on the contrary, tumor stabilization frequently occurs (40-80% of patients) (35,37,38), mainly in slow-growing pNETs with low proliferative rates (37,40,41).

In case of progressive NET or failure to achieve complete control of disease despite standard dose of SSAs, possible alternative options include a shortened interval (i.e., every 21 days) of SSA administration or high dose SSAs. 20-40% of patients require doses of octreotide-LAR >30 mg/28 mg (maximum dose approved by the FDA). Nevertheless, only few studies on dose escalation have been reported. However, the safety and tolerability of high dose LAR as well its potential for delaying the need for other invasive/potentially toxic interventions have been observed in some studies (42,43). In more detail, in a recent study by Ferolla *et al.*, a subset of patients with well differentiated progressive NET were administered SSAs every 21 days and this shortened schedule was able to re-institute control of clinical symptoms, to decrease level of circulating neuroendocrine markers and to significantly increase time to progression, as compared to the standard one (SSAs every 28 days). As regards advanced progressive midgut carcinoid tumours, Welin *et al.* described high-dose treatment with SSAs (i.e. octreotide pamoate 160 mg) as an effective therapeutic option, reporting improvement of the symptoms, and stabilisation of both hormone production and tumor growth in 75% of the patients (44). Finally, in case of uncontrolled symptoms despite standard SSA therapy or in case of carcinoid crisis, the use of immediate release octreotide as 'rescue' medication is suggested, with an initial dose ranging from 100 to 500 μg s.c., two to four times daily. A reasonable starting dose might be 150 μg s.c. three times daily, but some investigators prefer continuous s.c. infusion of octreotide by pump at a dose of 1,000-2,000 μg daily. The dose of immediate release octreotide may be escalated until maximum control of symptoms is achieved (21).

SSAs are generally well tolerated, and reported side effects are mild (i.e., pain at the injection site, and gastrointestinal symptoms) and usually resolve with prolonged treatment. Some more important long-term side effects have been described, such as the development of glucose intolerance/diabetes, steatorrhea, and cholelithiases, mainly biliary or gallbladder sludge, with only 1% of patients developing symptomatic gallbladder disease (45).

According to the ENETS 2012 guidelines SSAs may be a viable option in pNETs characterized by a slowly proliferative index (G1), whereas data on the efficacy of SSAs in NET G2 are still lacking (12). In metastatic non-functioning pNETs G3, SSA treatment is not recommended. Furthermore, the combination of SSAs with other anti-tumor therapies such as mammalian target of rapamycin (mTOR) inhibitors or anti-angiogenic agents is another possible approach, although there are no data showing the exact effect of their combination (46).

α-*interferon*

α-interferon (α-IFN) is a therapeutic option for palliation of hormonal symptoms, with the majority of patients (up to 71%) experiencing resolution of diarrhea or flushing. However, it is usually administered in combination with SSA therapy rather than as monotherapy. As regards its potential anti-growth effect, available data have reported a tumor stabilization in 30-80% of patients, but <15% of patients achieved a decrease in tumor size (2,18).

An important aspect to be considered during the administration of α-IFN is the frequent occurrence of side-effects, which may include mild manifestations, usually the most frequent, i.e., flu-like syndrome (80-97%), anorexia, weight loss (60%), and fatigue (51%), up to more serious ones, such as bone-marrow toxicity, hepatotoxicity, hyperlipidemia, autoimmune disorders, central nervous system and psychiatric disorders (18).

In conclusion, in case of G1 tumors, slowly progressive pNETs and/or somatostatin receptors-negative tumors, IFN treatment should be considered; due to the frequent occurrence of side effects, the administration of IFN must be tailored to the single patient (12,45).

Chemotherapy

According to ENETS Consensus guidelines, systemic chemotherapy using various cytotoxic agents (i.e., streptozotocin, doxorubicin, 5-fluorouracil, cisplatin, etoposide, dacarbazin) is recommended in pNETs, metastatic foregut NET G2, and in NEC G3 of any site (12).

PNETs are more responsive to cytotoxic chemotherapy when compared to low-grade carcinoid tumors, which may be due to reduced expression of methylguanine DNA methyltransferase (MGMT), a DNA repair enzyme, in pNETs compared to carcinoids (47).

Streptozotocin-based chemotherapies are still the gold standard for advanced progressive well-differentiated pNETs, although old (dacarbazin) or new (temozolomide, oxaliplatin) regimens have been shown to be effective therapeutic alternatives (46). According to available data, combinations of streptozotocin and 5-fluorouracil, with or without doxorubicin provide an objective response rate of 20-45%, whereas complete responses are rarely achieved with median responses of usually 6-20 months (12,18,48,49).

Recently, the combination of other cytotoxic agents, i.e., temozolomide and capecitabine has been described as a viable alternative option in the setting of advanced pNETs (50,51). Strosberg *et al.*, in their retrospective study, observed a partial response rate of 70% following the administration of temozolomide and capecitabine as first-line treatment for metastatic well-differentiated pNETs, with a median progression-free survival (PFS) rate of 18 months and the 2-year survival rate of 92% (50). However, phase III, prospective, randomized trials comparing streptozotocin-based therapies with another therapy (i.e., targeted therapies, chemoembolization, or alternative cytotoxic agent) in patients with pNETs are not available (46).

As regards high grade, poorly differentiated tumors (NEC G3), which behave similarly to small cell lung cancer from both biological and prognostic aspects, chemotherapy is almost exclusively based on platinum regimen with response rates of 42-67% for the combination of cisplatin and etoposide. According to available studies, the addition of paclitaxel to carboplatin and etoposide had no obvious advantage over doublet therapy (52).

Because chemotherapy determines several side effects and affects QoL, it is usually recommended for advanced inoperable well-differentiated (G1, G2) pNETs in case of failure of other treatments (i.e., biotherapy or targeted therapy), rapid tumor growth, poorly controlled symptoms, or poor prognosis, and in NEC G3 of any site (12,53).

Targeted medical therapy

mTOR Inhibitors

mTOR is a conserved serine/threonine kinase that regulates cell growth, proliferation, and metabolism in response to environmental factors (54). The mTOR protein is upregulated in several malignancies and plays an important role in pNETs (55).

Missiaglia *et al.* found that the genes phosphatase and tensin homolog and tuberous sclerosis 2, both

endogenous inhibitors of the mTOR pathway, behave as "oncosuppressors", and that their decreased expression occurs in several tumors, and correlates with a more aggressive tumor phenotype (56). These findings might be the rationale for the fact that mTOR inhibitors have reached phase II and III trials in neuroendocrine tumors.

Everolimus (RAD001, Afinitor, Novartis AG, Basel Switzerland), an orally active mTOR inhibitor, has been shown to have anti-growth effects in two phase II studies involving patients with pNETs (57,58) as well as in a phase III study (15). In the RADIANT-1 (RAD001 In Advanced Neuroendocrine Tumors) study, everolimus monotherapy was compared to everolimus plus octreotide depot in patients with advanced pNETs who developed progressive disease despite prior cytotoxic chemotherapy. According to this study, 84.4% of patients receiving combination therapy and 77.4% receiving monotherapy achieved tumor stability (58). In the RADIANT 3 study, patients with advanced pNETs were randomized to receive everolimus, at a dose of 10 mg per day, or placebo: everolimus was shown to significantly extend PFS from 4.6 months in the placebo arm to 11 months in the active treatment arm.

Among adverse events, stomatitis (62-64%), rash (37-49%), fatigue (31%), and diarrhea (34%) were the most frequent, although grade 3 or 4 adverse events did occur, including hematological and pneumological disorders, and hyperglycemia (15). The side-effects were generally manageable with dose reduction or drug interruption.

The possible role of everolimus in advanced pNETs is still matter of debating. According to ENETS 2012 guidelines, the use of everolimus is recommended in patients with advanced pNETs after the failure of systemic chemotherapy, whereas its administration as first-line therapy should be reserved for selected cases (12). In contrast, in the United States, everolimus might be used as a possible first line therapy for unresectable well-differentiated pNETs (27,59).

Another mTOR inhibitor (temsirolimus) seems to be a promising tool: according to a phase II study of metastatic NETs, this drug was reported to be associated with an intent-to-treat response rate of 5.6%, with a median time to progression of 6 months (60).

Angiogenesis inhibitors

NETs are highly vascular and frequently overexpress the vascular endothelial growth factor (VEGF) ligand and receptor (VEGFR).

Sunitinib (SU11248; Sutent, Pfizer, New York, NY) is an orally active, small molecule inhibitor of the tyrosine kinase activity of PDGFRs, VEGFR-1, VEGFR-2, c-KIT, and FLT3 (61). In a two-cohort phase II study, an objective response rate of 16.7% was associated with sunitinib monotherapy in pNETs (62). A multinational phase III study, comparing sunitinib (given at fixed dose of 37.5 mg daily) to placebo, showed a median PFS of 11.1 months in the sunitinib arm *vs.* 5.5 months in the placebo arm and an objective response rate associated with sunitinib of 9.3% (16). In a recent phase II study, Okusaka *et al.* observed a clinical benefit ratio of 75%, with a partial tumor response of 42% and stable disease of 33%, after the administration of 37.5 mg/day of sunitinib in patients with unresectable, metastatic pNETs (63).

The most frequent side effects associated to the administration of sunitinib included diarrhea (59%), nausea (45%), vomiting (33%), asthenia (33%), fatigue (32%); hypertension (10%) and neutropenia (12%) were the most severe reported side effects (16).

Sunitinib (Sutent®) has recently been approved by FDA and the European Medicines Agency (EMA) for the treatment of advanced and progressive well-differentiated pNETs (12). The ENETS 2012 guidelines conclude that, at present, both everolimus and sunitinib represent a novel therapeutic option in patients with advanced unresectable pNETs after failure of chemotherapy, and that they should be considered as first-line therapy only in selected cases (12). In contrast, according to the National Comprehensive Cancer Network (NCCN) guidelines (59) and a recent review of treatment of patients with metastatic pNETs (27), everolimus and sunitinib are suggested as a possible first-line treatment for unresectable well-differentiated pNETs.

Radiolabeled somatostatin analogues

The use of radiolabeled SSAs is a promising treatment option for unresectable or metastatic pNETs. A SRS is required prior to treatment, since radiolabeled SSAs are suitable only for patients with evidence of strong radiotracer uptake on SRS (at least as high as normal liver tissue) (5). In fact, peptide receptor radionuclide therapy (PRRT) with radiolabeled SSAs is based on the expression of somatostatin receptors by 60-100% of pNETs, which allows targeted radiotherapy to the tumor (64).

Two different radiolabels are most frequently used: 90Yttrium (90Y), a high-energy β-particle emitter with a maximum tissue penetration range of 12 mm and 177Lutetium (177Lu), which emits β-particles and γ-rays, and has a maximal tissue penetration of 2 mm.

Several studies involving patients with malignant NETs focused on treatment with 90Y-(DOTA0,Tyr3) octreotide, 90Y-(DOTA0,Tyr3) octreotate, or 90Y-(DOTA0) lanreotide and showed complete tumor response occurring in 0-6% of the patients, partial tumor regression in 7-37%, and tumor stabilization in 42-86% (17,63). As concerns 177Lu (DOTA0,Tyr3) octreotate in 510 patients with various malignant NETs, including 40% pNETs, a complete response was found in 2% of patients, partial tumor regression in 28%, minor tumor response in 1%, and tumor stabilization in 35% (65,66). Reported side effects of these therapies are mainly hematological, including myelodysplastic syndrome and nephrotoxicity.

The results obtained with DOTATATE Y-90 and 177lutetium-octreotate are very encouraging, although a direct, randomized comparison between the available treatments is lacking, thus PRRT is listed as an experimental or investigational treatment (4,20).

Liver-directed therapies

Several liver-directed therapies have been described, including radiofrequency ablation (RFA), cryoablation, alcohol ablation, hepatic arterial embolization, hepatic arterial chemoembolization, and might be applied either as a monotherapy or in combination with surgery (12,67).

There are no randomized trials which compare the effectiveness of various hepatic locoregional therapies and randomized studies comparing surgical to nonsurgical approach are lacking (12).

Ablative therapies

Ablation methods are generally reserved for unresectable metastases measuring less than 5-7 cm in diameter (17). RFA is usually performed to control both the symptoms related to liver metastases and the symptoms due to hormone secretion. RFA shows some limitations, i.e., tumors >5 cm in diameter are not suitable for RFA, although ablation may be used repeatedly within the same metastasis, and the number of tumor lesions should be limited (12). Moreover, in case of liver metastases near vital structures or at the surface of the liver, RFA might be contraindicated or technically not applicable. RFA generally shows low morbidity (15%), although, rarely, more serious complications can occur (i.e., bleeding, abscess formation) (25).

When RFA is contraindicated, cryotherapy might be a suitable alternative option. Furthermore, the combination of cryotherapy and RFA is considered a useful approach to limit complications (17). In case of small metastases or tumors located close to vital structures or vessels, percutaneous ethanol injection (PEI) could be taken into account (68), although RFA is usually preferred over PEI in neuroendocrine tumor setting.

Hepatic arterial embolization and hepatic arterial chemoembolization

Selective hepatic trans-catheter arterial embolization (TAE) or chemoembolization (TACE) with hepatic artery occlusion can be applied in the treatment of liver metastases from all types of NET G1/G2 (12). The rationale of their application is based on the relatively exclusive blood supply of neuroendocrine metastases from the hepatic artery, while the normal liver parenchyma gets its blood supply mainly (75%) from the portal vein (5).

In the presence of hepatic involvement of 50-75% by the tumor, portal venous occlusion, liver failure, post-surgical biliary reconstruction, or poor performance status TAE and TACE are not applicable (18).

TAE and TACE can both improve patient symptoms and reduce tumor size (68). In patients with malignant pNETs, a symptomatic and an objective response of 50-100% and 25-86% have been reported, respectively. The mean duration of the objective response was 6-45 months (69-71). There are non-randomized trials which prove that TACE is superior to TAE (12).

TAE and TACE show a mortality rate <6% and might determine some complications (i.e., post-embolization syndrome); furthermore, some serious complications rarely occur, including abscess of the liver, gallbladder necrosis, hepatic failure, and renal failure (27,72,73). Both TAE and TACE should be considered for palliative treatment in patients with hepatic-predominant pNETs that are not surgically resectable, particularly in case of functioning tumors poorly controlled by medical therapy. Due to the possible complications related to TAE and TACE, they should be performed only in experienced centers (12,20).

Selective internal radiation therapy (SIRT) using radioembolization with 90Yttrium (90Y) microspheres to the whole liver or an individual lobe with single or multiple

Table 2 Liver transplantation (OLT) is reserved only to selected cases. The table summarizes the main indications to OLT with inclusion criteria (I-V) (76)

Hormonal symptoms refractory to surgical or any other therapy
Non-functioning tumors and widespread liver disease
(I) Patients <55 years old
(II) Histological diagnosis of low-grade neuroendocrine tumor (with low expression of Ki-67, usually <10%)
(III) Primary tumor tributary of the portal vein, already removed with a curative resection
(IV) <50% of liver involvement
(V) Stable disease for at least 6 months during the pre-transplantation period

rations is another treatment modality that can be used even with extensive tumor replacement of normal liver and/or heavy pre-treatment. 90Y is a β-emitter with a half-life of 64.2 hrs and an average energy of 0.94 MeV, resulting in a tissue penetration of 2.5 mm and a maximum tissue range of 1.1 cm; therefore, the radiation administered is completely absorbed by the liver with reduced toxicity when compared to other therapies (5). A celiac angiogram is usually performed prior to the procedure to identify aberrant vessels that need to be avoided or embolized before treatment (5). According to available data, the mean overall objective response rate with 90Y was 55% (range, 12.5-89%) and stable disease was achieved in 32% (range, 10-60%) (74). Contraindications to the use of SIRT include inadequate liver reserve, the presence of aberrant vessels and consequent excess shunting to the gastrointestinal tract or to the lung, the inability to isolate the liver arterial tree from the gastric and small bowel branches, and the presence of a compromised portal vein (75). Reported side effects of SIRT seem to be less severe than those of chemoembolization or embolization, which is another important aspect to be considered in the therapeutic decision (75).

Liver transplantation

In case of failure of both surgical and medical therapies, OLT may be an alternative option for selected patients with metastatic pNETs. Patients <50 years old who are free of extra-hepatic tumors or have a well-differentiated tumor with low levels of Ki-67 index are considered to be the best candidates for OLT (12). There are some specific criteria to be fulfilled prior to consider OLT as a therapeutic option, and these are known as "Milan criteria" in case of NETs: an histological diagnosis of low-grade neuroendocrine tumor (with low expression of Ki-67) regardless of the presence or absence of syndrome; primary tumor located in the pancreas or intermediate, thus tributary of the portal vein, already removed with a curative resection; <50% of liver involvement; stable disease for at least 6 months during the pre-transplantation period; patients <55 years. In case of small-cell carcinoma and high-grade neuroendocrine carcinomas (G3), other medical/surgical conditions contraindicating liver transplantation or tumors which are not tributary of the portal vein system, OLT cannot be considered as a viable option (76).

In conclusion, OLT should be taken into account in young patients suffering life-threatening hormonal disturbances or with non-functioning pNETs and diffuse liver metastases refractory to all other treatments. The selection of patients according to "Milan criteria" in case of NETs is mandatory (12).

The main indications to OLT with inclusion criteria are summarized in *Table 2*.

Conclusions

Therapeutic options for metastatic pNETs are expanding, although surgery still remains the gold standard for treatment, in order to provide both extended survival and symptom relief.

PNETs and gastrointestinal NETs are different either from a prognostic or from a therapeutic aspect. PNETs have a 5-year survival rate of 30-60%, whereas gastrointestinal tumors show a survival rate of 60-90% (13). Moreover, the recent advances in targeted therapies suggest a different response of pancreatic and intestinal tumors. Long-acting SSAs have been reported to delay disease progression in well-differentiated midgut NETs (39). On the other hand, everolimus and sunitinib have recently demonstrated their anti-proliferative effect in well-differentiated NETs of pancreatic origin, but they are not approved for extra-pancreatic NETs (15,16).

The multidisciplinary approach is mandatory in neuroendocrine setting; furthermore, taken into account

the more benign behavior of NETs when compared to other malignancies, both the preservation of the QoL of the patient and the personalization of the therapy according to tumor' and patient's features are needed.

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