Review Article

Current treatment status in pancreatic neuroendocrine neoplasms

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Abstract: Pancreatic neuroendocrine neoplasms (P-NENs) are a group of pathologically and clinically heterogeneous tumors. In the past several decades, the incidence has been increasing. In 2010, the WHO presented a new classification dividing P-NENs into well-differentiated neuroendocrine tumors (NETs) and poorly-differentiated neuroendocrine carcinomas (NECs). Surgery is the primary and most important treatment for P-NENs, and is also the only possible curative procedure. By the 2018 NCCN guideline, observation can be considered for <1 cm, low-grade asymptomatic nonfunctional P-NETs. And for patients who are not suitable for surgery, somatostatin analogues, targeted therapy, radionuclides, ablation therapies, (chemo)embolisation and chemotherapy should be considered to improve and maintain a good quality of life. More than one hundred years has passed since termed, and in recent years, more and more molecule mechanism about P-NENs have been discovered. With the addition of several new agents, survival improved over the time. All this made P-NENs great promise.

Keywords: Pancreatic neuroendocrine neoplasm (P-NEN); treatment; surgery; somatostatin analogues

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Introduction

Neuroendocrine neoplasms (NENs) once called carcinoid tumors, endocrine tumors or neuroendocrine tumors (NETs) are a group of pathologically and clinically heterogeneous tumors. These tumors mostly occurred in lung and gastroenteropancreatic (GEP) tract (1). In the past several decades, the incidence has been increasing in both east and west nations, partly due to the wide application of modern imaging and endoscopic technologies (2-10). According to whether these tumors can secrete hormones and amines, causing carcinoid syndrome and other clinical syndromes, they can be classified to functional NENs (F-NENs) and non-functional NENs (NF-NENs). And all the NENs have malignant potential and the malignant potential further depends on tumor site, degree of differentiation and extension of the tumors (11). The 5-year survival rate was 30–80% for all patients, 60–100% for localized disease, 40–55% for regional disease, 19–30% for distant metastases (8,12).

Pancreatic neuroendocrine neoplasms (P-NENs), commonly be called pancreatic endocrine tumors, insulinoma, gastrinoma or glucagonoma, comprise <2% of all pancreatic tumors (8,13). They may produce hormones, such as insulin, gastrin, glucagon, vasoactive intestinal peptide (VIP) and so on, causing special symptoms called carcinoid syndrome. And about half of the P-NENs present clinical symptoms (14). Of all these functional p-NENs, gastrinomas and insulinomas are the two most common, while the others are always considered together as a group called rare functional P-NENs (RFTs) (14-16).

In 1907, Oberndorfer first differentiated NENs as carcinoid from carcinomas. And because of the rareness and lacked knowledge of these tumors, people tended to lump them together in classification assessment and treatment for one hundred years (17,18). During this period, there was no

published unified nomenclatures and classifications that can be accepted by both clinicians and pathologists (19,20).

In order to standardize the stratification and management procedures, in 2010, the WHO adopted the classification originally proposed by the European Neuroendocrine Tumor Society (ENETS) from 2004 and 2007 (12,21-24), and presented a new classification. According to this new classification system, all tumors with a neuroendocrine differentiation called NENs (25). And all GEP-NENs can be subdivided into the well-differentiated NETs and the poorly-differentiated neuroendocrine carcinomas (NECs). Furthermore, according to different definitions of proliferation by the mitotic count and/or the Ki-67 index, NENs can be graded into three types, low grade (grade 1, G1), intermediate grade (grade 2, G2) and high-grade (grade 3, G3). In general, both G1 and G2 NENs are considered as NETs, and G3 NENs are considered as NECs. According to this classification, tumors with Ki-67 index more than 20% or mitotic rate more than 20 per 10 high power fields are defined as G3. Meanwhile, specific TNM classification was also introduced.

However, in recent years, several studies highlighted heterogeneity that the 2010 WHO G3 category might be composed of two different entities, according to their cellular histomorphology, nuclear mitotic rate, Ki67 index, somatostatin receptor expression, plasma CGA (chromogranin) and NSE (neuron specific enolase) levels, response to platinum-based chemotherapy and prognosis (26-31). Therefore, in 2017, the new WHO classification introduced a new category of well-differentiated pancreatic NETs (WD-pNETs) G3, different from poorly differentiated pancreatic NECs (PD-pNECs) G3 (32-34).

The 5-year survival rate of P-NENs was 80% for all stages, 60–100% for localized disease, 40% for regional disease and 29% for distant metastases (12,35). The long-term disease-specific survival (DSS) of surgical resected P-NENs is greater than 50% at 20 years (36).

Treatment

As a kind of rare and special tumors, the treatment of both WD-pNETs and PD-pNECs depending on the symptoms, stage of disease, degree of uptake of radionuclide, and histological features of these tumors.

Surgery

Surgery has been the focus of therapy and remains the primary and most important treatment for P-NENs, and is also the only possible curative procedure. And indications for surgery depend on clinical symptoms, tumor size and location, malignancy and metastatic spread (12,37-41). The first TNM staging system for P-NENs was proposed in the year 2006 by the ENETS (23). Currently, two different staging systems proposed by the ENETS and AJCC (American Joint Committee on Cancer) are widely used in managing P-NENs (23,42), and tumors with superior mesenteric artery and/or celiac axis and/or common hepatic artery encasement as well as those with superior mesenteric vein occlusion are considered unresectable (41).

All resectable functional or non-functional P-NENs are recommended for surgery. The type of surgical procedure including pancreaticoduodenectomy, distal pancreatic resection, tumor enucleation and enucleation in combination with resection depending on the location of the tumor. As to whether this surgery is performed by the traditional open or laparoscopic route depending on the discretion of each designated specialist pancreatic surgery centre (38). Meanwhile lymph node dissection is recommended for malignant P-NENs, for example tumors with pancreatic membrane invasion or lymph node metastasis.

Insulinomas comprise approximately 35–40% of functional P-NENs (13), and malignant insulinomas account for only about 5–10% of all insulinomas (43). Therefore, all resectable insulinomas should be removed surgically in spite of the tumor size, and 85–90% patients could be cured with surgery (44).

In the past decade, whether surgery should be applied in patients with localized small asymptomatic P-NETs is controversial. Recently, several studies have reported that nonfunctional P-NETs with diameter less than 2 cm were more likely to grow slowly over many years, with low malignancy, less or no node and liver metastasis, fewer vascular or peripancreatic invasion and satisfactory prognosis, so nonoperative management is enough (45-47). Meanwhile, there were also analyses indicated that those small tumors can display aggressive behavior, such as late metastases or recurrence, and resection was recommend to get better survival (48-53). And in 2017, a consensus statement published by the Chinese Study Group for Neuroendocrine Tumors (CSNET) except for some selected patients with NF-pNETs <1 cm, incidentally discovered and unacceptable surgical risks, all others with NF-pNETs ≤2 cm should undergo tumor resection and careful postoperative surveillance (54). Recently, by the

2018 NCCN guideline, observation can be considered for <1 cm, low-grade asymptomatic nonfunctional P-NETs base on the study by Sadot *et al.* in 2016 (55,56).

For the metastatic P-NENs, surgery should also be considered in both functioning and non-functioning tumors. It has been reported that primary tumor resection is associated with prolonged survival for all metastatic GEP-NENs, including P-NENs (57).

For GEP-NENs and P-NENs, liver was the most common site of distant metastases (11/14, 78.57%) (58). And when metastasis is limited to the liver, curative surgery should be applied if complete resection of both primary and metastases is available. Meanwhile, when 90% liver metastatic mass can be successfully removed, surgery should also be undertaken, with the purpose to control clinic symptom and to promote survival (12,38). However, surgical resection for liver-metastatic lesions should be avoided for non-functional liver-metastatic p-NENs with unresectable primary tumor (invading the celiac axis, the superior mesenteric artery, or adjacent organs, such as stomach, spleen, colon and adrenal gland) (59).

Medical treatment

Depending on the slow-growing feature of these tumors, patients often survived for a long period despite having metastases. Therefore, for patients who are not suitable for surgery, somatostatin analogues, targeted therapy, radionuclides, ablation therapies, (chemo)embolisation and chemotherapy should be considered to improve and maintain a good quality of life. When possible, liver transplantation may be considered in some special patients with no extrahepatic metastases.

One special and important feature of GEP-NENs is the expression of somatostatin (SST) receptors. Totally, five SST receptors were expressed in these tumors and the order of expression has been assessed as follows: SST2, SST5, SST1, SST3, SST4 (60). The use of SST analogues to control clinical symptoms by inhibiting the secretion of tumor products has been more than thirty years (61,62). At the same time, the function of inhibiting tumor growth was also demonstrated (63,64).

Native SST, as an inhibitory hormone with a half-life of just 2–3 min, inhibits the release of hormones, including those causing carcinoid syndrome (65). However, the short half-life of native SST limited its use and led to the development of synthetic analogue of SST, including short-acting analogues (octreotide, lanreotide or vapreotide), long-acting analogues [octreotide long-acting release (LAR), and lanreotide autogel].

The short-acting analogues, such as octreotide with the half-life of approximately 1.5 h, need to be administered thrice daily by subcutaneous or intravenous injection. And the long-acting analogues, such as octreotide LAR, can be given once every four weeks (66,67).

In recent years, basic researches have demonstrated the antiproliferative activity of tumor cell *in vitro* (68,69). Meanwhile, several retrospective or prospective large clinic trials have also demonstrated the efficacy and safety of long-acting SST analogues in the treatment of well-differentiated GEP-NET, including well-differentiated PNETs (70-73). And based on minimal adverse effects of somatostatin analogs, combinations of somatostatin analogs with other biotherapies or molecular targeted therapies, and peptide receptor-targeted radionuclide therapy were introduced to get ideal efficacy (74,75). For example, ^{90}Y-edotreotide was used to treat patients' refractory to octreotide (76).

NENs exhibited the nature of highly vascular (77), and vascular endothelial growth factor (VEGF) is crucial to angiogenesis in pancreatic NETs (78,79), therefore angiogenesis inhibition has been considered as a treatment modality in this disease. Sunitinib which has been identified as a potent inhibitor of VEGFR-1 and VEGFR-2, is a novel oral multitargeted tyrosine kinase inhibitor with antiangiogenic and antitumor activities. Finally, the phase 1, 2 and 3 study all proved the antitumor activities of this drug in advanced P-NENs (80-83).

In 2007, Zitzmann *et al.* demonstrated the antiproliferative and apoptotic effects of RAD001 (everolimus) in NET cells *in vitro* (84). The following phase 2 and phase 3 studies subsequently confirmed the single-agent activity of the mammalian target of rapamycin (mTOR) inhibitor everolimus in patients with P-NET (85-87). By the final overall survival (OS) data of the RADIANT-3 phase 3 study, for those advanced, progressive, low or intermediate-grade pancreatic NET patients, everolimus showed a median OS of 44 months, the longest OS reported in a phase III study for this population (87).

More recently, with minimal adverse effects of new drags, combination of two or more agents have been applied to get better result for those advanced P-NETs, such as everolimus and octreotide LAR (88-92), everolimus and sunitinib (93), combination of bevacizumab, pertuzumab, and octreotide LAR (94), combination of fluorouracil, doxorubicin, and streptozocin (95,96).

Temozolomide an alkylating agent once used in metastatic

melanoma and glioma, has been applied as monotherapy or combined with other agent in the treatment of advanced GEP-NENs for more than decade (97-99). More recently, the combination of Temozolomide and Capecitabine, a precursor of fluorouracil, has been proved effective in treat metastatic, well or moderately differentiated P-NENTs (100-103). And this CAPTEM regimen is well tolerated and relatively safe. In 2018, a meta-analysis including fifteen studies with 384 individuals reported that this regimen can get similar or slightly higher PFS (progression-free survival) compared with other regimens in treating NENs, with disease control rate of 72.89% (104). While, the reported overall response rates of single-agent temozolomide was 8% to 25% by retrospective studies (97,99).

The poorly differentiated GEP-NEC accounting about 35–55% of all NEC originating from the lung. This frequency might differ by organ in the tract, with only about 7% of the P-NENs have were NEC (105-107).

In recent years, most molecular discoveries and therapeutic advances have been based on studies of well differentiated low-grade NETs, but less is known about high-grade NEC (108). And, the treatment strategies for extrapulmonary NEC are often extrapolated from the treatment paradigm for small cell lung cancer (109,110).

For localized P-NECs, curative surgery is usually recommended (111). However, even for those with apparently localized disease surgery alone is rarely curative (112). Additional systemic chemotherapy has been reported to improve the survival of resected or unresectable advanced NECs (108). Etoposide and cisplatin (EP) regimen has always been considered the first line treatment for poorly differentiated NECs, since Moertel *et al.* reported the favorable response in treating GEP-NECs in 1991 (113).

However, the response-time of the EP regimen in treating NECs is short. So several other different chemotherapeutics have been explored in the past few years, such as IP regimen (cisplatin plus irinotecan) (114), FOLFIRI regimen (irinotecan, folinic acid and fluorouracil) (115), three-drug regimen of paclitaxel, carboplatin and etoposide (116,117).

Summary

More than one hundred years has passed since termed, and there is a general consensus that NENs are going mainstream (18). In recent years, more and more molecule mechanism about P-NENs have been discovered, and in 2017 whole-genome sequencing of 102 primary P-NENs was performed (118). With the addition of several new agents, survival improved over the time in recent years (2,8). All this made P-NENs great promise.

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Footnote

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