Gastroenteropancreatic neuroendocrine tumors: recommendations of Turkish multidisciplinary neuroendocrine tumor study group on diagnosis, treatment and follow-up

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Abstract

Gastroenteropancreatic neuroendocrine tumors (GEPNETs) are a relatively rare, heterogeneous group of diseases in which important advances have been observed in the diagnosis and treatment as well as in our understanding of the biology and genetics of the disease in recent years. Given the insufficient scientific data available on evidence-based management of GEPNETs and the differences in circumstances in individual countries, a multidisciplinary study group was established to provide guidelines for the management of GEPNETS. This study group consisted of a medical oncologist, endocrinologist, surgeon, pathologist, gastroenterologist, and a nuclear medicine specialist, who aimed to prepare a practical guide in the light of existing scientific data and international guidelines, to be used in common clinical practice.

Key words: neuroendocrine tumor, guideline, consensus, diagnosis, treatment.

Introduction

Gastroenteropancreatic neuroendocrine tumors (GEPNETs) are a rare, heterogeneous group of tumors, most frequently located in the stomach, pancreas, small and large intestine, and rectum [1]. Since NETs may originate and effect various organ systems, a multidisciplinary approach including specialists from different medical fields is necessary. Therefore, an expert group, consisting of specialists from medical oncology, gastroenterology, endocrinology, nuclear medicine, pathology and surgery, was formed to establish a consensus report for the management of GEPNETs. Although there are several existing global guidelines, availability of treatment options and patient profiles may be different in individual countries, which creates a necessity to develop national guidelines in the light of existing global guidelines. The experts systematically reviewed the reported scientific data, international guidelines, and recently presented

clinical trials, in order to prepare a set of practical recommendations for the multidisciplinary management of GEPNETs in Turkey [2–5].

Epidemiology

Gastroenteropancreatic neuroendocrine tumors may occur at any age; the highest incidence is among individuals > 50 years of age. In patients with multiple endocrine neoplasia (MEN) type 1 or von Hippel-Lindau (VHL) or other genetic syndromes, the age at diagnosis is 15–20 years lower than those with sporadic GEPNETs. Although the incidence of cancer is decreasing overall, GEPNET incidence has been steadily increasing in the last few years, with an estimated incidence of 5.25/100,000 in the year 2004 [6, 7]. Gastroenteropancreatic neuroendocrine tumor incidence is slightly higher in men compared to women (5.35/100,000 vs. 4.76/100,000). Currently, the general incidence of GEPNET is expected to reach 8/100,000. The prevalence of the disease is however estimated to be much higher, and it ranks second after colorectal cancers among gastrointestinal tumors in the USA [7]. In Turkey, GEPNETs are not specifically included in the cancer registry system; therefore, incidence and prevalence data on GEPNETs are inadequate in Turkey. The GEPNET registry study data will provide multi-centric, both retrospective and prospective epidemiological data related to this disease in Turkey and in the region [8]. However, certainly it is necessary to develop a formal country-specific database for GEPNETs in Turkey. This registry system should be compatible with the European Neuroendocrine Tumor Society (ENETS) European Patient Registry system and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) tumor registry system so that the system may provide comparative data and help ensure its sustainability.

Molecular biology

There is a wide range of clinical and genetic variation between adenocarcinoma and neuroendocrine tumors of the pancreas. Although there are important differences between all GEPNET sub-types, it is practical to classify these tumors in 2 main groups – pancreatic NETs (PNETs) and gastrointestinal NETs (GI-NETs) – because PNETs and GI-NETs have different genetic and molecular biological characteristics [9, 10]. Most of the GEPNETs are sporadic, however, they may be associated with familial genetic neuroendocrine tumor syndromes. The main types of these hereditary syndromes are MEN syndromes (MEN-1 and MEN-2), neurofibromatosis type 1, VHL syndrome, tuberous sclerosis and Carney complex. The recognition of these syndromes is not only important for proper patient management but can also help his/her family members to be identified for screening for GEPNETs and/or concomitant tumors and diseases. Mutations in the MEN-1 gene are seen not only in MEN-1 syndrome but also in sporadic PNETs as well. In fact, a 40% mutation rate of the MEN-1 gene has been reported in one study exploring PNETs. Similarly, genetic changes related to the ATRX/DAXX gene and the mammalian target of rapamycin (mTOR) pathway were also reported in PNETs. Moreover, there may be mutations in chromosome 18 in small intestine NETs. In a study with new generation gene sequencing, somatic mutation rates were found to be low in 48 patients with small intestine NETs; the analysis showed that the most frequent changes are found in the PI3K/Akt/mTOR signaling pathway, the transforming growth factor (TGF)-β pathway (through alterations in *SMAD* genes), and the *SRC* oncogene [11]. However, a genetic difference was not determined between sporadic and familial small intestine NETs. Among GEPNETs, genetic changes and carcinogenesis pathways are best clarified in MEN type 2 syndrome; activated mutations in the RET oncogene lead to the development of the tumor and this mutation demonstrates a genotype-phenotype correlation. Therefore, genetic counseling should be provided in suitable centers to identify cases with a possibility of familial inheritance, and multidisciplinary studies on genetic alterations relevant to the diagnosis and treatment of the disease should be supported.

Pathology and diagnosis

Gastroenteropancreatic neuroendocrine tumors show common phenotypic characteristics. Therefore, they show similar immunoreactivity to pan-neuroendocrine markers, chromogranin A and synaptophysin. Apart from these two markers, although less specific, neuron-specific enolase (NSE), CD56 and CD57 can be used to identify rectum NETs and poorly differentiated NETs.

All tumors diagnosed as GEPNETs should be graded based on the mitotic count and Ki-67 index [12, 13]. Therefore, it is mandatory to determine the proliferation index by immunohistochemical assessment of Ki-67 (MIB-1) in the tumor tissue. For the pathological classification the WHO 2010 classification concerning the terminology of neuroendocrine tumor/carcinoma has been accepted (Tables I–IV) [1]. According to the WHO/ENETS grading system: mitosis < 2/10 high power field (HPF) and/or Ki-67 ≤ 2%: grade 1; mitosis 2–20/10 HPF and/or Ki-67 3–20%: grade 2; mitosis: > 20/20 HPF and/or Ki-67 > 20% grade 3 (Tables I–IV) [12, 13].

Table I. NET grading

Mitosis	Ki-67%	ENETS/WHO	Grade
< 2	< 3	NET	I
2–20	3–20	NET	II
> 20	> 20	NEC (small cell or large cells)	III
		Mixed adenoendocrine carcinoma (MANEC)	

Table II. ENETS and AJCC TNM staging for pancreatic NET

	ENETS TNM	AJCC/UICC TNM
T1	Limited to pancreas, < 2 cm	Limited to pancreas, < 2 cm
T2	Limited to pancreas, 2–4 cm	Limited to pancreas, > 2 cm
T3	Limited to pancreas > 4 cm; or tumor invasion of duodenum or common bile duct	Tumor invasion of peripancreatic tissue. Not involving major vascular invasion (truncus coeliacus, A. mesenterica superior)
T4	Tumor invasion of any adjacent structure or involving major vascular invasion	Involving major vascular invasion

Table III. ENETS and AJCC TNM staging for Appendix

	ENETS TNM	AJCC/UICC TNM
T1	Invasion of muscularis propria; ≤ 1 cm	T1A: ≤ 1 cm T1B: > 1–2 cm
T2	≤ 2 cm and < 3 mm invasion of mesoappendix/ subserous layer	> 2–4 cm or invasion of caecum
T3	> 2 cm > 3 mm invasion of mesoappendix/subserous layer	> 4 cm or invasion of ileum
T4	Invasion of peritoneum/other organ	Invasion of peritoneum/other organ

Table IV. ENETS and AJCC TNM staging for gastric NET

	ENET	AJCC
TX	Primary tumor cannot be assessed	Primary tumor cannot be assessed
T0	No evidence of primary tumor	No evidence of primary tumor
Tis	< 0.5 mm	Confined mucosa, < 0.5 mm
T1	Lamina propria or submucosa and ≤ 1 cm	Tumor confined to mucosa and 0.5 mm or > 1 cm or Invades submucosa and < 1 cm
T2	Muscularis propria or subserosa or > 1 cm	Muscularis propria or > 1 cm
T3	Tumor penetrates serosa	Tumor invades subserosa
T4	Tumor invades adjacent structures	Tumor invades visceral peritoneum (serosa) or other organs or adjacent structures

All GEPNETs should be considered as potentially malignant, and the use of the term "benign" should be particularly avoided with GEPNETs. Immunohistochemical assessment of specific hormone expression is not routine in pathological evaluation. In addition, immunohistochemical detection of hormone expression in the tumor tissue (insulin, glucagon, vasoactive intestinal peptide (VIP) etc.) does not indicate that the tumor is functional.

Grading of the patients should be combined with organ specific TNM. There are some differences in the ENETS and WHO classifications, and the debate is on-going on this issue [14]. Accordingly, the below criteria considering the other current guidelines should be available in each pathology report [15]. Localization, size and invasion depth of the GEPNET, number of mitoses in 10 HPF and Ki-67 score, immunophenotypic properties (at

least chromogranin A and synaptophysin) and surgical margin of the excision/resection material should be included in the report.

Tumors classified as a single group as grade 3 tumors under the heading of neuroendocrine carcinoma using only the mitotic count and Ki-67 rate as the determinant criteria may be well differentiated, poorly differentiated or undifferentiated histologically, and may have small or large cell morphology. Given the differences in the clinic course and treatment of these different entities, the cut-off values of the Ki-67 index and mitotic count should be revised in the near future [16, 17].

Staging

Staging and pathology reporting should be based on the WHO 2010 classification and the International Union Against Cancer (UICC) TNM 7th edition (Tables I–IV) [18]. Organ specific TNM classifications by the WHO 2010 and ENETS classifications show differences regarding GEPNETs located in the stomach, appendix and pancreas. For GEPNETs originating from these organs, both ENETS and WHO 2010 classification systems can be used for reporting, but it should be indicated in the pathology report.

Somatostatin receptor imaging (^{111}In Oct or preferably Ga-68) should be performed for preoperative staging in patients diagnosed with well-differentiated GEPNETs. Positron emission tomography (PET) – computed tomography (CT) imaging with Ga-68 labeled peptide is more sensitive than somatostatin receptor scintigraphy (SRS) and may change the clinical approach in 20–30% of the patients [19]. According to the localization of the primary tumor, CT and/or magnetic resonance imaging (MRI) should also be used for diagnosis and staging. Ultrasound and endoscopic ultrasound should be used when necessary as complementary examinations. Standard PET with 5-fluorodeoxyglucose (FDG) administration is not sensitive in well-differentiated GEPNETs, but can be used in diagnosis, staging and follow-up of aggressive, poorly differentiated GEPNETs [19–23]. In addition, it may be helpful to demonstrate the transformation to aggressive biological behavior [24, 25]. The FDG uptake on FDG PET/CT is a powerful and independent prognostic factor in patients with neuroendocrine tumors. A prospective trial of 98 patients with neuroendocrine tumors demonstrated the strong prognostic value of presence and intensity of FDG uptake. Patients with FDG avidity were associated with a significantly higher risk of death (hazard ratio of 10.3) [26].

Thus far, the role of novel tracers in GEPNET has only been studied in clinical research and single center experience [27, 28].

Patients with GEPNET should have panendoscopy (esophagogastroduodenoscopy, colonoscopy, double-balloon enteroscopy and capsule endoscopy) performed according to the localization of the primary tumor, and also patients with an unknown primary tumor should have panendoscopy performed. In patients with GEPNETs of unknown primary site, the pancreas, appendix, ileum, lung and stomach should be examined first. These patients should primarily undergo MR enteroclysis, somatostatin receptor imaging with Ga-68, SRS and biopsy of suspected sites. If these methods do not yield to the detection of primary results, appropriate advanced tests should be performed.

Treatment

The site of primary disease (especially pancreatic and extrapancreatic origin), grade, stage and whether the disease is symptomatic (functional) or not are the primary factors important in treatment decision-making. Therefore, surgery, non-surgical local ablation methods, somatostatin analogues, interferon, chemotherapy, targeted agents and peptide receptor radionuclide therapy (PRRT) can be used in suitable patients [6, 29].

Surgery

Gastrointestinal NETs: Surgery is the only potentially curative treatment modality. Surgery should be considered for patients with early stage disease, in patients with locoregional and resectable metastatic disease, and in symptomatic patients. Surgery is the most effective method in the treatment of isolated liver metastases. Resection of the primary tumor and metastasectomy should primarily be considered in all suitable patients. Liver metastasectomy is the standard treatment in cases with 3 to 5 metastatic lesions limited to one lobe, and in those with multiple metastases with each metastatic lesion < 5 cm at suitable sites. In other circumstances, each patient should be individually evaluated. In some series including selected patients, the 5-year survival rate reached up to 80%. Primary tumor resection has a favorable effect on survival even in patients with unresectable metastatic disease because there is a risk for mesenteric fibrosis, obstruction, and vascular occlusion/thrombosis in small intestine NETs [30]. These patients are therefore suitable for primary tumor resection and lymph node dissection. However, small intestine resection may lead to short bowel syndrome.

Pancreatic NETs: Curative surgery with metastasectomy should also be considered in patients with metastatic PNETs that are potentially resectable. There is also evidence for the benefit of resection of the primary in patients with unresect-

able hepatic metastases from PNETs as well [30]. The type of surgery for the pancreatic primary depends on the primary tumor site such as pancreatico-duodenal resection (Whipple surgery), distal pancreatic resection or resection in combination with enucleation. It is necessary to remove an adequate number of lymph nodes in these patients. Laparoscopic resection is not suitable because of the necessity of lymphadenectomy and attentive evaluation for invasion and metastasis.

G3 pancreatic tumors or poorly differentiated gastrointestinal neuroendocrine cell carcinomas (NECs) may not be suitable for surgery because these tumors generally show extensive metastasis at the time of diagnosis [29–32].

Surgery can also be beneficial in patients with local recurrence and for symptom control. However, surgery is available in only 20% of patients, and the recurrence rate after surgery is very high in metastatic disease. The benefits of adjuvant treatment after potentially curative surgery have still not been demonstrated. Although there are no studies examining adjuvant postoperative treatment in poorly differentiated or high grade NEC, their aggressive behavior justifies the use of adjuvant therapy in most cases. In this case cisplatin or carboplatin and etoposide combination chemotherapy is recommended. Sequential radiation can also be considered in cases where the risk of local recurrence is thought to be higher than usual [33].

Liver transplantation: The standards of liver transplantation have not yet been established. Five-year survival after liver transplantation is below 50%, and disease-free survival is below 30%. Recurrence rate, and morbidity and mortality rates are increased after liver transplantation. The best candidates for liver transplantation include patients below 55 years of age, patients with low-grade tumors, resected primary tumors, tumors with liver invasion < 50%, no extra-hepatic disease and those without disease progression in the last 6 months. The likelihood of extrahepatic lymphatic or vascular spread (for example to the distal rectum or lung) of the primary disease should not be high in these patients [6, 34, 35].

Non-surgical loco-regional therapy

Radiofrequency ablation (RFA)

Radiofrequency ablation is used intraoperatively during percutaneous and laparoscopic interventions or during laparotomy in patients not suitable for metastasectomy. Although RFA can be used for lesions < 5 cm, the best results are achieved in lesions with a maximum diameter of 3 cm. There is no definite agreement on the number of lesions for which RFA can be applied. However, the chances of success decrease if there are more than 4 lesions. Radiofrequency ablation is not recommended for use if the number of lesions > 10. Radiofrequency ablation can provide tumor and symptom control [36–39]. However, in patients with unfavorably located lesions or with previous Whipple surgery RFA should be used cautiously.

Microwave/cryotherapy and percutaneous alcohol injection

Microwave and cryotherapy are alternative local ablation methods that may be used in suitable centers by experienced teams. Percutaneous alcohol injection should not be considered if the other methods are available [6, 40].

Transarterial embolization (TAE) and transarterial chemoembolization (TACE)

Liver metastases of NETs are tumors characterized with high vascularization. Transarterial embolization (TAE) and transarterial chemoembolization (TACE) or radioembolization may decrease the tumor burden and hormone secretion in patients not suitable for surgery or RFA and medical treatment. In patients who show progression after systemic treatment, or in those whose symptom control cannot be maintained, TAE, TACE or radioembolization may be used depending on the individual patient characteristics and availability [41–48].

Transarterial chemoembolization is performed at 4–6 week intervals. In bilobar disease, stepwise embolization can be applied to each lobe. Most frequently, lipiodol, foam particles, iodinated contrast, and cyanoacrylate are used for embolization [41–43]. Superiority of beads used in TACE has not been demonstrated clearly. The objective response rates with TACE are widely variable; however, disease stabilization and symptom control rates are high. During TACE, a selected chemotherapy regimen such as doxorubicin, cisplatin, 5-fluorouracil and mitomycin-C can be used via transarterial catheterization [41–44]. The most important complications in these patients are liver abscess, sepsis, pleural effusion, hepatorenal failure, and hepatic infarction. Moreover, as the risk of complication is greatly increased in patients with previous Whipple surgery, TACE should be performed only in selected conditions; it should not be used in the following conditions: massive or diffuse hepatic involvement, if metastasis involves > 50% of the liver, hepatic failure, portal vein invasion, serum bilirubin > 2–3 mg/dl and serum transaminases > 100 IU/l. Transarterial chemoembolization should be performed cautiously in patients with portal vein thrombosis and only suitable patients should be selected. Superselective embolization with low dose chemotherapy should be used in these patients [41–43].

Radioembolization

Radioembolization is also known as selective internal radiation therapy (SIRT). Y^{90} embedded resin microspheres (SIR-Spheres, Sirtex Medical Ltd, Lane Cove, Australia) or Y^{90} embedded glass microspheres (TheraSphere, MDS Nordion Inc., Ontario, Canada) are infused through the hepatic artery [44–47]. Radioembolization can be used in unresectable lesions not suitable for RFA and in progressive liver metastasis unresponsive to medical treatment. The conditions necessary for radioembolization include sufficient liver reserve (bilirubin < 2–3 mg/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 5 times, albumin > 3 mg/dl), an ECOG performance status score < 2, life expectancy > 3 months, and normal prothrombin and partial thrombin time [42–45]. Its superiority to chemoembolization is debatable; however, it should be preferred to embolization or chemoembolization in patients with mild and moderate liver dysfunction or portal vein thrombosis, as it does not cause ischemic hepatitis [6, 45–48].

Peptide receptor-radionuclide radiotherapy (PRRT)

Peptide receptor-radionuclide radiotherapy can be used in patients with well-differentiated low-grade NETs having positive somatostatin receptor imaging [49, 50]. Better tumor responses are achieved with increased uptake of the radioactive peptide in the tumor. Radioisotope molecules that can be used for this purpose are primarily Lu^{177} and less frequently Y^{90}. In^{111} is no longer preferred. ^{177}Lu-DOTA-Tyr3-octreotate is preferred as it has less renal toxicity and higher sst2 affinity. PRRT can be considered independently from the primary tumor site in both functional and non-functional tumors. PRRT should be used when first line medical treatment is not successful in GI-NET but at later stages as a salvage after somatostatin analogues, targeted therapies (sunitinib/everolimus) and/or chemotherapy in PNET [6, 49]. However, response rates are higher in PNETs in comparison to small intestine NETs [6, 49, 50].

Medical treatment

Treatment of clinical symptoms

Clinical symptoms may vary according to whether the tumor is functional or non-functional, and depending on the tumor's localization site and size. The main clinical symptoms are pain, obstruction, diarrhea, hypoglycemia symptoms, hyperglycemia, weight loss, and carcinoid syndrome findings. The majority of these findings can be eliminated by treatment of the tumor. If carcinoid syndrome symptoms are present, somatostatin analogues, interferon, symptomatic treatment for diarrhea, mTOR inhibition and other treatments can be applied [51–56].

Somatostatin analogues

As the half-life of natural somatostatin hormone is very short, somatostatin analogues with longer half-lives are currently used [51–53]. These are short- and long-acting octreotide and lanreotide. Pasireotide is also being studied in GEPNET patients [51]. Symptom control by somatostatin analogues improves the patient's quality of life, and enables the control of disease progression. For symptom control, short-acting somatostatin analogues at 100–150 µg doses should be used 2–3 times daily for at least 2 weeks; thereafter, monthly depot forms of somatostatin analogues (octreotide LAR 20–30 mg, lanreotide 60–120 mg) should be used. Short-acting forms should be continued for 2 additional weeks in these patients. If symptom control cannot be achieved, additional doses of short-acting somatostatin analogues can be used and the octreotide dose can be increased to 1500 µg daily. Again, the dose of the depot form may gradually be increased (octreotide 40–60 mg) in these patients. Asymptomatic patients may receive the depot form of the drug directly [51–54].

Somatostatin analogues, octreotide LAR and lanreotide can be used in functional and non-functional small intestine tumors and well-differentiated PNETs for anti-proliferative purposes. Somatostatin analogues are the recommended first line of treatment in non-functional and functional progressive G1/G2 NETs. However, independent of the site of origin, somatostatin analogue treatment is not recommended in metastatic NEC G3. In addition, independent of the origin of the primary tumor and potential microscopic metastases, somatostatin analogues are not indicated in the adjuvant treatment of NET G1/G2. The Clarinet study showed the anti-tumor efficacy of somatostatin analogues in the treatment of non-functional tumors and PNETs [57–61].

Interferon

Interferon (IFN) has antiviral and anti-tumor activity; it has been used alone and in combination with chemotherapy and somatostatin analogues [6, 54, 61, 62]. Interferon-α has been most widely studied. A pooled analysis of trials on IFN-α among patients with GEPNETs demonstrated that approximately 40% of patients had biochemical responses; the symptomatic response with IFN ranges from 40% to 70%, which is comparable to that observed with octreotide and lanreotide [62]. The objective tumor response is approximately 10%. Thus, while somatostatin analogues and IFN have similar effects on symptom control, IFN

has greater anti-proliferative activity. However, IFN has a slow onset of action and poor favorable tolerability; therefore, IFN can be better used as a second-line approach in patients with functioning NETs and low proliferation. Combination of IFN-α with somatostatin analogues might have a synergistic effect; however, this combination has net been tested in large prospective studies, data come from a limited number of small studies, usually underpowered and with no prespecified primary endpoint. Furthermore, the clinical benefit of this synergistic effect may not be significant. Therefore, interferon-somatostatin analogue combination can be used only in some selected cases as salvage therapy, but not as a standard therapy [61, 62].

Systemic treatment

Systemic chemotherapy

Systemic chemotherapy is more effective in patients with a rapidly progressive disease or a tumor with a high proliferation rate and aggressive pathological features. Streptozotocin (STZ), chlorozotocin, 5-fluorouracil (5-FU), capecitabine, dacarbazine (DTIC), gemcitabine, temozolomide, and doxorubicin, as a single agent, are reported to have limited activity with response rates ranging from 0% to 50% [63–69].

Combination chemotherapy has been shown to be more effective than single agent chemotherapy in PNETs. Compared with STZ alone, 5-FU and STZ combination yielded a higher response rate (36% vs. 63%) and a longer median survival rate [70, 71]. Furthermore, the addition of doxorubicin to STZ also improved the response rate in patients with advanced PNETs [72]. The response rate ranges from 8% to 60%. In retrospective studies response rates reaching up to 70% with the temozolomide and capecitabine combination have been reported [73, 74]. In a more recent prospective phase II study a response rate of 43% was observed in a group of patients with well-differentiated NET including pancreas, gastrointestinal tract, pituitary and medullary thyroid tumor [75]. Likewise, oxaliplatin, irinotecan and fluoropyrimidine combinations can be used in the salvage treatment of GEPNETs, particularly in PNETs. However, randomized phase III studies are needed. Still, chemotherapy can be used as salvage therapy in selected patients with well-differentiated grade 1 gastrointestinal NETs and in patients with grade 2 tumors.

Cisplatin plus etoposide combination is the standard first-line treatment of poorly differentiated NETs, independent of the primary tumor site and whether it is a surgically excised grade 3 GEPNET, while the combinations of streptozotocin plus 5-FU or streptozotocin plus doxorubicin are usually suggested as a first-line treatment in well-differentiated NETs with disease progression [76, 77]. Temozolomide plus capecitabine, irinotecan-based (irinotecan plus cisplatin or 5-FU) regimens can be used as second line treatment in patients with high grade PNETs [78, 79].

There is a strong need for data to define the role of adjuvant treatment in low or intermediate degree tumors that are surgically resected [6].

Targeted treatments

mTOR inhibitors

Mammalian target of rapamycin is a serine/threonine protein kinase that is a part of the phosphatidylinositol 3′ kinase (PI3K)-AKT signaling pathway. RADIANT-2, a randomized double-blind, placebo controlled, multicenter phase III study, evaluated the effects of octreotide combined with everolimus or placebo in patients with advanced NETs. After promising results with everolimus, RADIANT-3, a randomized double-blind, placebo controlled, multicenter phase III study of octreotide combined with everolimus or placebo in patients with advanced PNETs, was designed. Patients were randomized to receive either everolimus 10 mg/day plus best supportive care or placebo plus best supportive care. The majority of the patients had well-differentiated or moderately differentiated tumors. Median progression-free survival (PFS) was 11.4 months in the treatment arm and 4.6 months in the placebo arm (HR = 0.35; $p < 0.0001$). The most common side effects in the RADIANT trials were stomatitis followed by infections and pneumonitis. Therefore, the investigators concluded that everolimus is safe and well tolerable in patients with NETs [56, 80–82].

With the current available clinical data, use of everolimus at a dose of 10 mg/day as a single agent is indicated in the first and second line treatment and salvage treatment of progressive well-differentiated (grade 1–2) PNETs. Although the endpoint stated in the study could not be reached in gastrointestinal NETs, everolimus can be used in the treatment of all well-differentiated neuroendocrine tumors if appropriate as suggested in the ESMO guidelines [2, 56].

Tyrosine kinase inhibitors

Sunitinib is a multi-targeted tyrosine kinase inhibitor, inhibiting VEGFR-1, -2, and -3, as well as platelet-derived growth factor (PDGF), KIT, and FLT3. A phase III study was performed to compare sunitinib at a continuous daily dose of 37.5 mg to a placebo. The study, which was discontinued early following the planned interim analysis after the enrollment of 171 patients, demonstrat-

ed a median PFS of 11.1 months in the sunitinib arm vs. 5.5 months in the placebo arm. The objective response rate in the sunitinib arm was 9.3% [83]. With these findings, sunitinib can be used in the treatment of well-differentiated PNETs with a Ki-67 score ≤ 5% as first-line, second-line and salvage treatment [83, 84]. However, in a phase II study no definitive benefit was found in gastrointestinal NETs [85].

Pazopanib is an oral tyrosine kinase inhibitor targeting VEGFR, PDGFR and KIT with demonstrated clinical activity in NETs [86]. A phase II study showed that pazopanib might be clinically beneficial after everolimus and sunitinib use in the treatment of NETs [87].

Published data so far do not support the use of other tyrosine kinases such as sorafenib, gefitinib, imatinib or vatalanib in GEPNETs [88–95].

Bevacizumab

Bevacizumab is a monoclonal antibody which neutralizes vascular endothelial growth factor. Although data do not support the routine use of bevacizumab yet, it has been shown that it may be used in selected PNET cases [95]. Single agent efficacy of the other tested drugs, thalidomide and endostatin, has not been demonstrated [6].

Response evaluation and follow-up

The follow-up of patients who have been completely resected with surgery or endoscopy can be done at 3- to 6-month intervals. Response evaluation in those that receive systemic treatment should be performed at 3-month intervals [2]. The method that should be used depends on primary disease site, the course of the disease and the best imaging method at diagnosis [96]. In the routine follow-up of patients with no signs and symptoms of the disease, performance of SRS may be recommended at the earliest at 12 months; however, SRS should be used along with the other required methods in the treatment response evaluation and follow-up of advanced stage patients. Follow-up and response evaluation during PRRT should be done after staging at 12-month intervals. It is appropriate to perform scintigraphic

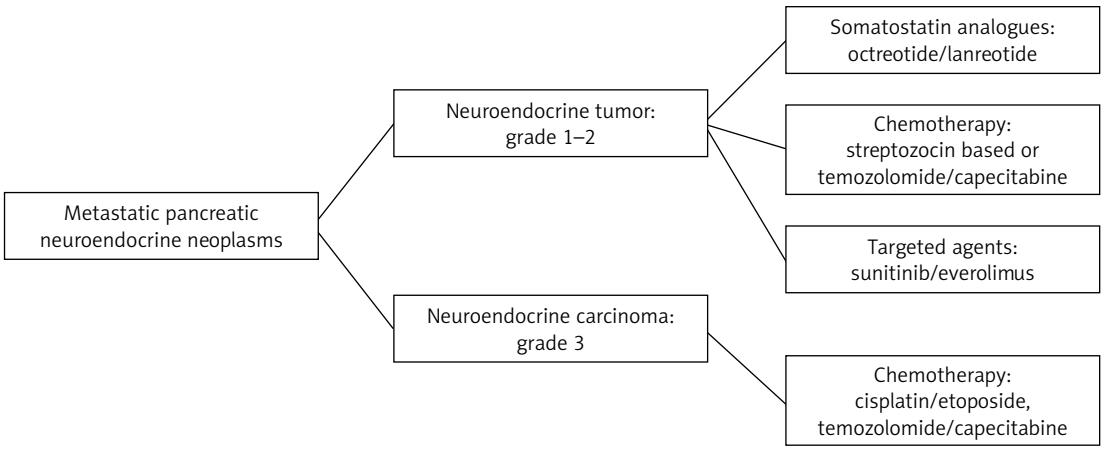

Figure 1. First line systemic treatment options for unresectable and/or metastatic pancreatic neuroendocrine neoplasms

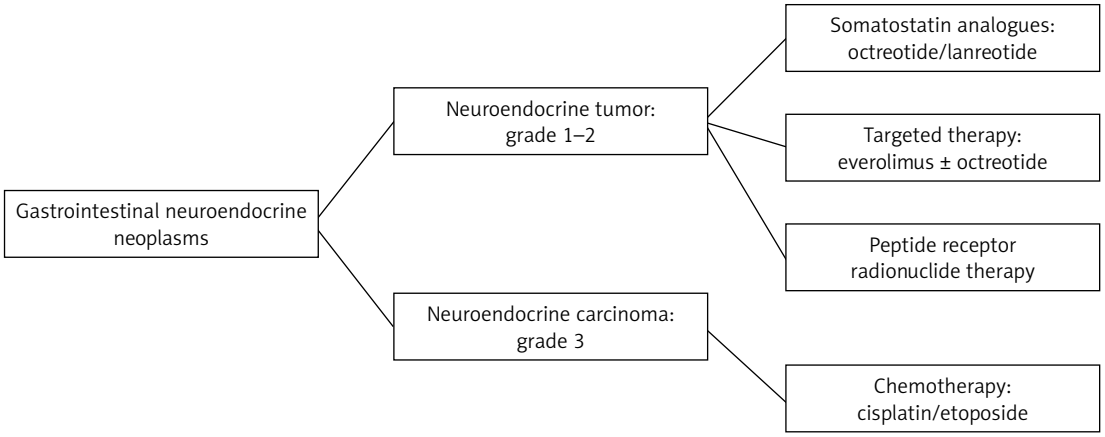

Figure 2. First line systemic treatment options for unresectable and/or metastatic gastrointestinal neuroendocrine neoplasms

imaging at 3-month intervals for follow-up of the PRRT response so that the functional response can be determined before anatomic imaging [96, 97].

Conclusions

With the availability of newer treatment options improving survival in advanced NETs, treatment should be individualized depending on the prognostic and predictive factors (Figures 1, 2). Meanwhile there is no established adjuvant therapy after curative surgery, except for high grade NEC. All GEPNET patients should be evaluated, treated and followed in a multidisciplinary setting in experienced centers. Since these tumors are still considered as rare tumors, national and international patient registries are necessary to obtain further epidemiological and clinical data to improve our understanding of this heterogeneous disease.

Conflict of interest

Suayib Yalcin has had advisory board role in Novartis, Roche, Pfizer, Amgen and speaker Bureau role for Gen ilaç, Novartis, Roche, Pfizer and travel grant from Roche and Pfizer, and research grant from Celgene.

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