Chapter 9
Molecular Targeted Therapy for Gastroenteropancreatic Neuroendocrine Tumors

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Abstract Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are generally considered rare tumor. According to the recent studies, the number of patients had been increasing and frequently diagnosed as advanced stages. Surgery is the only possible way to cure GEP-NENs. However, the indication of surgical treatment for the patients with advanced GEP-NENs is limited, and for those patients other therapies such as radiofrequency ablation, transarterial chemoembolization, and/or systemic medical treatment are selected. Molecular targeted therapy is one of the promising treatments for low-grade or well-differentiated GEP-NENs. Phase III randomized studies of molecular targeted agents, such as somatostatin analogues, mTOR inhibitor, and tyrosine kinase inhibitor, had been conducted, and those studies demonstrated the antiproliferative effect in patients with GEP-NENs. Octreotide long-acting release, somatostatin analogue, was approved for gastrointestinal NENs. Lanreotide Autogel, another somatostatin analogue, was approved for GEP-NEN. Everolimus, mTOR inhibitor, was approved for GEP-NENs. Sunitinib, tyrosine kinase inhibitor, was approved for pancreatic NENs. Despite these advances, some tumors show intrinsic resistance to these targeting therapies. The arrival of novel treatment, which gives more options for the patient with GEP-NENs, is desired.

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9.1 Epidemiology of Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NENs)

Neuroendocrine neoplasms (NENs) are generally considered rare tumors [1]. According to the Surveillance, Epidemiology, and End Results (SEER) study, a US epidemiological database, the number of patients has been increasing; the incidence rate of the disease increased fivefold from 1.09 per 100,000 people in 1973 to 5.25 per 100,000 people in 2004 [2]. Ito et al. reported the result of Japanese epidemiological study: a 1.2-fold increase in the number of patients, who received treatment for pancreatic NENs (P-NENs), from 2005 to 2010 and a 1.8-fold increase in the number of patients with gastrointestinal NENs (GI-NENs) [3]. (Table 9.1).

NENs are generally considered more indolent than other gastrointestinal malignancies. However, GEP-NENs are frequently diagnosed at advanced stages. According to the SEER study, 28% of patients with NENs had distant metastasis at diagnosis, 15% of patients with gastric NENs, 30% of patients with jejunal/ileal NENs, 5% of patients with rectal NENs, and 64% of patients with P-NENs [2]. According to the Japanese epidemiological study, 6.0% of patients with GI-NENs exhibited distant metastasis at initial diagnosis and 19.9% of patients with P-NENs [3]. (Table 9.2).

Table 9.1 The trends epidemiology of NENs in SEER data and Japanese epidemiological study

	1973	1999	2004	2005	2010
SEER data[a]					
Incidence rate of all-NENs (per 100,000 population)	1.09	4.73	5.25		
Japanese epidemiological study[b]					
Total number of patients with treated for p-NEN				2845	3379
Overall prevalence of p-NENs (per 100,000 population)				2.23	2.69
Incidence rate of p-NENs (per 100,000 population)				1.01	1.27
Total number of patients with treated for GI-NEN				4406	8088
Overall prevalence of GI-NENs (per 100,000 population)				2.45	6.42
Incidence rate of GI-NENs (per 100,000 population)				2.10	3.51

[a]Yao [2]
[b]Ito [3]

Table 9.2 Distant metastasis of NENs in SEER data and Japanese epidemiological study

	Percentages of distant metastasis (%)	
SEER data (1973–2004)[a]		
Pancreas	64	
Gastric	15	
Duodenum	9	
Jejunum/ileum	30	
Rectum	5	
Japanese epidemiological study (2010)[b]		
Pancreas		19.9
Foregut (expt. pancreas)		6.0
Midgut		9.8
Hind gut		3.5

[a]Yao [2]
[b]Ito [3]

Table 9.3 WHO 2010 classification of GEP-NENs

Classification	Mitotic Count (per 10 HPF)	Ki-67 index (%)
NET G1	<2	<3
NET G2	2–20	3–20
NEC	>20	>20

WHO World Health Organization, *GEP-NENs* gastroenteropancreatic neuroendocrine neoplasms, *NET* neuroendocrine tumor, *NEC* neuroendocrine carcinoma

9.2 Pathological Classification

The 2010 World Health Organization (WHO) classification classified GEP-NENs into three categories (neuroendocrine tumor grade 1(NET G1), neuroendocrine tumor grade 2 (NET G2), and neuroendocrine carcinoma (NEC)) on the basis of Ki-67 proliferation index and/or mitotic count. A mitotic count of <2 per 10 high-power fields (hpf) and/or a Ki-67 index <3% corresponds to NET G1, a mitotic count of 2–20/10 hpf and/or a Ki-67 index of 3–20% to NET G2, and a mitotic count of >20/10 hpf and/or a Ki-67 index >20% (grade3) to NEC (Table 9.3). NET G1 and NET G2 are generally more indolent, less aggressive course than NEC [4, 5]. According to this 2010 WHO classification, both poorly differentiated small cell carcinoma and large cell neuroendocrine carcinoma (LCNEC) correspond to NEC. This classification system is pathologically simple and very useful to standardize diagnosis and treatment procedures. However, mitotic count and Ki-67 index are higher in small cell carcinoma or LACNEC than well-differentiated tumors. Recent data also suggests that it may not be correct to consider all NEC as a single entity, and some researchers have proposed that well-differentiated subtype

of NEC should be designated as NET G3 (neuroendocrine tumor grade 3) to distinguish from small cell carcinoma or LCNEC [6–9]. Some P-NENs show discordance between Ki-67 index and mitotic count; well-differentiated P-NEN that is grade 3 by Ki-67 is significantly less aggressive than poorly differentiated NECs [6]. In other study, grade 3 GI-NEN with a Ki-67 index <55% were less responsive to first-line platinum-based chemotherapy [9].

9.3 Treatments for GEP-NENs

9.3.1 Indication of Medical Treatment

Surgical treatment is only the possible way to cure the GEP-NENs and the indication of surgical treatment should be considered for all patients with GEP-NENs. Liver resection is often performed in the well-differentiated (G1 or G2) GEP-NEN patients with hepatic metastasis, depending on the tumor number, size, and location of the metastatic lesions and the extent of primary tumor [10]. The rationale of liver resection is provided by studies showing longer survival after resection of liver metastases, and the clinical effectiveness of liver resection can be partly explained by intrinsic slow progression of well-differentiated GEP-NENs [11–13]. Surgical treatment is the preferred method whenever possible; however, the patients with unresectable advanced GEP-NENs need radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and/or systemic medical treatment. The goals of treatments in the patients with unresectable disease are to palliate tumor-related symptoms and prolong life span. Figure 9.1 shows treatment options in the advanced locoregional or metastatic disease. There are multiple systemic treatment options available including somatostatin analogues, molecular targeted agents, cytotoxic chemotherapy, and peptide receptor radiation therapy (PRRT). However, the rarity of this disease and the number of prospective randomized trials are limited, and the most therapeutic recommendations are based on the expert opinions.

9.3.2 Cytotoxic Chemotherapy

Cytotoxic chemotherapy has been used to treat the patients with unresectable progressive GEP-NEN for more than 50 years. Streptozocin (STZ) was approved in the USA as a cytotoxic antitumor drug for symptomatic or advanced P-NEN in 1982. STZ combined with doxorubicin (DOX) or fluorouracil (5-FU) has been used as a first-line chemotherapy for GEP-NENs based on several clinical trials including

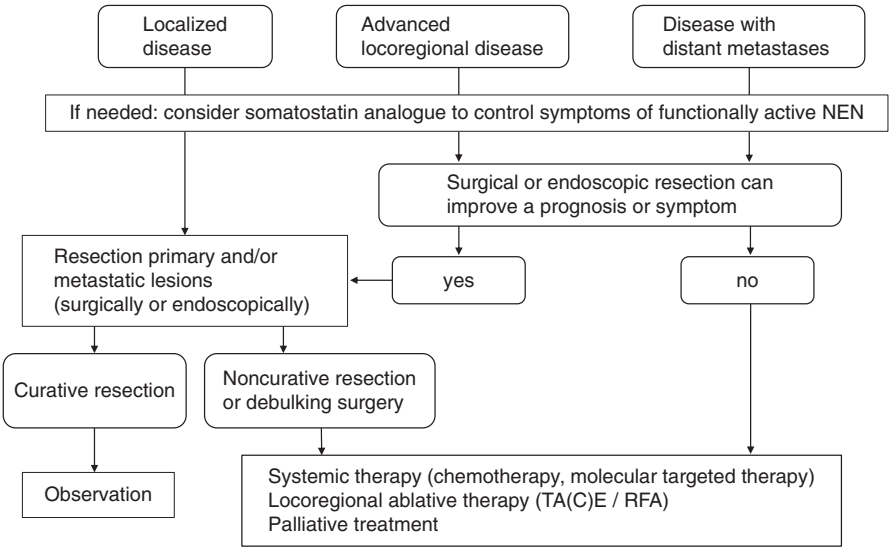

Fig. 9.1 A treatment flowchart of gastroenteropancreatic neuroendocrine neoplasms

randomized clinical trials [14–19]. However, this result was not reproduced in similar studies conducted later [20]. The combination of another alkylating agent temozolomide and capecitabine showed high response in metastatic P-NEN. Response rate of 70% was achieved, and median progressive-free survival was 18 months [21]. In the treatment of P-NENs, chemotherapy has been demonstrated to have both palliative and antitumor effects, though evidence regarding survival is still conflicting. The positioning of cytotoxic chemotherapies is still under discussion.

9.3.3 Molecular Targeted Therapies

In the recent basic and clinical research, somatostatin analogues, mammalian target of rapamycin (mTOR) inhibitors and tyrosine kinase inhibitors appear to have great potential for the treatment of advanced GEP-NENs [22–29]. Octreotide, lanreotide, sunitinib, and everolimus are the drugs evaluated within placebo-controlled studies in GEP-NENs and had evidence for the treatment. Molecular targeted treatments for advanced NENs have been approved on the basis of their antiproliferative effects, and some clinical trial data of molecular targeted therapies show the prolongation effects of progression-free survival among the patients with advanced, metastatic GEP-NENs (Table 9.4).

Table 9.4 Phase III randomized trials of molecular targeted therapy for well- to moderately differentiated advanced or metastatic GEP-NENs

Trial	Agent	Primary tumor sites functionality	Number of patients actual/placebo	Median PFS (months) actual/placebo	HR *p*-value
PROMID (2009)	Octreotide LAR 30 mg i.m., q4w	Midgut functional/nonfunctional	42/43	14.3/6.0 (TTP)	0.34 (0.20–0.59) $p = 0.000072$
CLARINET (2014)	Lanreotide autogel 120 mg s.c., q4w	Gastrointestinal/pancreas nonfunctional	101/103	Nr/18.0	0.47 (0.30–0.73) $p < 0.001$
RADIANT 3 (2011)	Everolimus 10 mg/day p.o.	Pancreas nonfunctional	207/203	11.4/5.4[a]	0.34 (0.26–0.44) $p < 0.001$
RADIANT 4 (2016)	Everolimus 10 mg/day p.o.	Lung/gastrointestinal nonfunctional	205/97	11.0/3.9	0.48 (0.35–0.67) $p < 0.00001$
Sunitinib (2011)	Sunitinib malate 37.5 mg/day p.o.	Pancreas functional/nonfunctional	86/85	11.4/5.5	0.42 (0.26–0.66) $p < 0.001$

[a]Review by central adjudication committee

GEP-NENs Gastroenteropancreatic neuroendocrine neoplasms, *LAR* long-acting-release, *i.m.* intramuscular injection, *s.c.* subcutaneous injection, *p.o.* oral administration, *PFS* progression free survival, *TTP* time to tumor progression, *HR* hazard ratio

9.4 Molecular Targeted Therapy for Advanced GEP-NENs

9.4.1 Somatostatin Receptor and Somatostatin Analogues

Somatostatin and its synthetic analogues bind to G-protein couple receptors and inhibit both secretion and growth of NENs. Somatostatin analogues have been used both for the diagnosis and therapy for NENs. Five distinct somatostatin receptor subtype genes (SSTR1–5) were cloned [30]. GEP-NENs, except insulinoma, express SSTR2 in 80–100% cases, whereas insulinomas have a lower incidence of SSTR2 expression [31]. Well-differentiated GEP-NENs usually express higher frequency of SSTRs than poorly or undifferentiated GEP-NENs [32].

The mechanisms of somatostatin receptor signaling and regulation have been elucidated. The well-known somatostatin action is inhibitory effect on secretion. This inhibitory effect is mediated by coupling of SSTR to Gi/Go proteins, and

subsequently G-protein activation leads to reduction of second messengers, cyclic AMP, and cytosolic calcium. The reduction of second messengers by somatostatin leads to inhibitory effect on hormone release [33, 34]. Another important somatostatin action is inhibition of NEN cell proliferation, and this effect can be mediated by two general signaling pathways. One pathway is activation of protein tyrosine phosphatases. The dephosphorylation of specific substrates is proposed to counteract growth factor stimulated tyrosine kinase activity and then to inhibit mitogenic signaling pathways [35–38]. The second pathway is SSTR inhibition of adenylyl cyclase. The inhibition of adenylyl cyclase leads to a reduction in cyclic AMP levels and thus to changes in cAMP response element-binding protein (CREB) and extracellular receptor kinase (ERK) signaling [39–41], although the role of this pathway is still under discussion.

As of now, three somatostatin analogues, octreotide, lanreotide, and pasireotide, are available. However, pasireotide, a novel universal somatostatin ligand, is not approved for the treatment of GEP-NENs. Focused on the antiproliferative role of somatostatin analogues, there are two phase III randomized studies, the PROMID study and the CLARINET study, which was published. Both study are placebo-controlled, double-blind, prospective, randomized study. In the PROMID study, the antitumor effect of octreotide long-acting release (LAR) on the well-differentiated metastatic NENs was examined [22]. This study included only midgut NENs. In this study, 85 patients were randomly assigned to either placebo or octreotide LAR 30 mg intramuscularly monthly until tumor progression or death. The primary end point of this study was time to tumor progression (TTP), and secondary end points were survival time and tumor response. The significant difference of TTP was observed between the octreotide LAR group and placebo group (14.3 months and 6 months, $P = 0.000072$), and antiproliferative efficacy was demonstrated [22]. Subgroup analyses of this study suggested that the antiproliferative effect was influenced by hepatic tumor burden and resection of the primary tumor [22]. In the CLARINET study, the antitumor effect of extended-release aqueous-gel formulation of lanreotide (Autogel) on the SSTR-positive, well, or moderately differentiated (Ki-67 index of <10%) metastatic GEP-NENs were examined [23]. Primary tumors were located in the pancreas, midgut, or hindgut or were of unknown origin. Two hundred four patients were randomly assigned to either placebo or lanreotide Autogel 120 mg deep subcutaneously once every 28 days for 96 weeks. The primary end point of this study was progression-free survival (PFS), and secondary end points were overall survival, quality of life, and safety [23]. The significant difference of PFS was observed between the lanreotide Autogel group and placebo group (median not reached and median of 18.0 months, $P < 0.001$). The estimated progression-free survival at 24 months was 65.1% in the lanreotide Autogel group and 33.0% in the placebo group. No significant difference in quality of life or overall survival was observed [23]. These two studies demonstrate the antiproliferative effect with long-acting somatostatin analogues in patients with NENs.

9.4.2 *mTOR Pathway and mTOR Inhibitor*

In most cases, upregulation of mTOR pathway is prevalent in P-NENs. mTOR is a serine/threonine protein kinase, belongs to the family of the phosphatidylinositol (PI) 3-kinase (PI3K)-related protein kinases, and plays a critical role in cell growth, proliferation, and migration [42]. mTOR is associated in two distinct complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). Modulation of downstream mTORC1 effectors promotes protein synthesis and cell proliferation and inhibits autophagy. mTORC2 is a main modulator of cell growth. mTORC2 is directly upstream of AKT and activation of AKT stimulates downstream of mTORC1. mTORC2 also activates protein kinase c (PKC), a member of the MAPK/ERK signaling pathway. Upregulation of the PI3K/mTOR/AKT pathway is a common feature of proliferative disorder [43–45] (Fig. 9.2).

Rapamycin, a kind of mTOR inhibitor, was found as an antibiotic produced by the bacterium *Streptomyces hygroscopicus*. There are three rapamycin analogues (rapalogs) that are synthesized, CCI779, AP23573, and RAD001 (everolimus). Based on the phase II studies of everolimus, which demonstrated promising antitumor effect of everolimus in GEP-NENs [46, 47], two randomized double-blind placebo-controlled phase III trials, RADIANT 3 and RADIANT 4, was conducted. In RADIANT 3 trial, 410 patients, who had advanced low-grade or intermediate-grade P-NENs with radiologic progression within the previous 12 months, were randomly assigned to receive everolimus (207 patients) or placebo (203 patients) [26]. Everolimus significantly prolonged the progression-free survival (PFS)

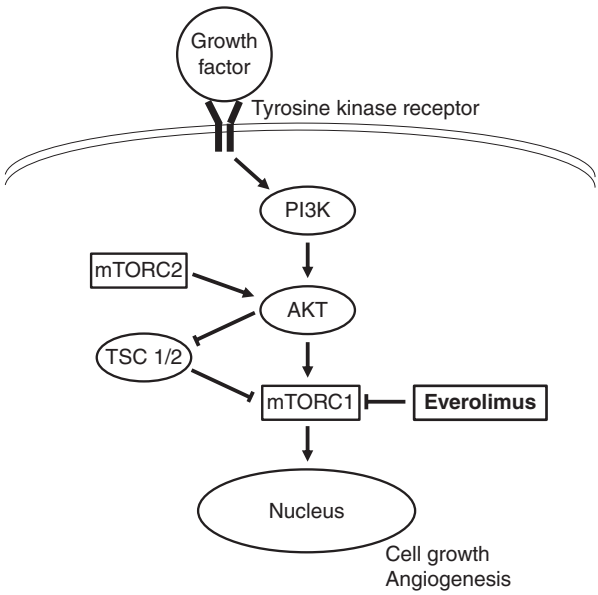

Fig. 9.2 mTOR signaling pathway. Everolimus suppresses mTOR complex 1 (mTORC1), which leads to cell growth and angiogenesis

compared with placebo (median PFS, 11.0 months vs. 4.6 months; hazard ratio for disease progression or death with everolimus, 0.35; 95% CI, 0.27–0.45; $p < 0.001$) [26]. In RADIANT 4 trial, 302 patients, who had advanced well-differentiated non-functional NEN of the lung, gastrointestinal tract origin, were randomly assigned in a 2:1 ratio to receive everolimus (205 patients) or placebo (97 patients) [27]. Everolimus significantly prolonged the PFS compared with placebo (median PFS, 11.0 months vs. 3.9 months; hazard ratio for disease progression or death with everolimus, 0.48; 95% CI, 0.40–0.67; $p < 0.00001$) [27]. The result of RADIANT 3 trial and RADIANT 4 trail indicates that the treatment with everolimus markedly extended the PFS in patients with advanced NEN of the lung, gastrointestinal tract, or pancreas origin. Based on the above two randomized trials, everolimus was approved in the USA, European countries, and other countries.

9.4.3 Angiogenesis and Tyrosine Kinase Inhibitor

Well-differentiated NENs are characterized as high vascular tumors and express high level of vascular endothelial growth factor (VEGF) [48]. Malignant P-NENs widely express platelet-derived growth factor receptors (PDGFRs) α and β, stem-cell factor receptor (c-kit), and VEGF receptor (VEGFR)-2 and VEGFR-3 [49, 50]. Sunitinib is a multi-target anti-angiogenetic tyrosine kinase inhibitor and it blocks VEGFR, PDGFR β, c-KIT, FlT-3, and RET [26] (Fig. 9.3). A phase II trial investigated the efficacy of sunitinib in both carcinoid tumors (41 patients, originated in the lung, stomach, small bowel, appendix, colon, or rectum) and P-NENs (66 patients) [51]. Patients were treated with sunitinib 50 mg/day for 4 weeks, followed by a 2 weeks off treatment. This trial suggested that sunitinib had antitumor activity in P-NENs; however, definitive effective could not be seen in carcinoid tumors [51]. Based on this phase II trial, one randomized double-blind placebo-controlled phase III trial with sunitinib was conducted. In this phase III trial, 171 patients who had advanced well-differentiated P-NEN were randomly assigned to receive sunitinib (86 patients) or placebo (85 patients) [28]. In sunitinib group, patients received best supportive care with once-daily sunitinib at a dose of 37.5 ng/day. The dose reduction (37.5 mg instead of 50 mg) was due to the increased rate of grade 3 fatigue in

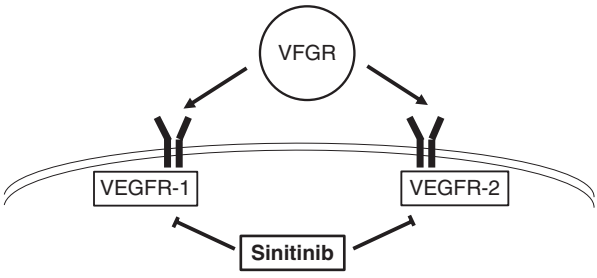

Fig. 9.3 Sunitinib suppresses VGEFR-1 and VEFGR-2

the phase II study [28, 51]. Sunitinib significantly prolonged the PFS compared with placebo (median PFS, 11.4 months vs. 5.5 months; hazard ratio for disease progression or death with everolimus, 0.42; 95% CI, 0.26–0.66; $p < 0.001$) [28]. Based on the above phase III trial, sunitinib was approved for P-NENs.

9.5 Conclusions

For the treatment of well-differentiated (NET G1/G2) GEP-NENs, promising targeted agents, such as octreotide, lanreotide, everolimus, and sunitinib, have emerged on the bases of randomized phase III trials. Despite these advances, some tumors show intrinsic resistance to these targeting therapies. Various other clinical trials of GEP-NENs are being conducted. The arrival of novel treatment, which gives more options for the patient with GEP-NENs, is desired.

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