Review article

Navigating the treatment landscape in gastroenteropancreatic neuroendocrine neoplasms

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ABSTRACT

Gastroenteropancreatic neuroendocrine neoplasms are a large and very diverse group of neoplasms. They are becoming a burning clinical problem because of increasing frequency and diagnosis in the advanced state. The treatment landscape has been changed over the last years. Treatment choice depends on many factors such as the tumor's type, location, aggressiveness, and hormone-producing capabilities. The main goals of treatment are long-term symptomatic control, antitumor effect, and improvement of the quality of life. The results of the PROMID and CLARINET trials have augmented fundamental position of somatostatin analogs. Our understanding of the biology, genetics of the neoplasms has improved considerably in the last several decades and the spectrum of available therapeutic options is rapidly expanded. The current evidence-based treatment options include everolimus, sunitinib, peptide receptor radionuclide therapy, and chemotherapy. Treatment practice changed as a result of high-quality phase 3 clinical trials which shaped current guidelines; multiple retrospective studies which raised new questions and attempted to fill some of the data gaps. Here we review the treatment options for gastroenteropancreatic neuroendocrine neoplasms, discussing important diagnosis and biomarker-related factors, safety of therapy with special insight into cardiac safety, as well we looked at promising investigative therapies.

Key words: gastroenteropancreatic neuroendocrine tumors, treatment options, neuroendocrine tumors

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INTRODUCTION

The treatment landscape for the management of neuroendocrine neoplasms (NENs) has evolved significantly over the past years. In the last decade, treatment practice changed as a result of high-quality phase 3 clinical trials as well as multiple retrospective studies. They focused on the long-term symptomatic control, antitumor effect and quality of life, since patients with neuroendocrine tumors often present metastases at diagnosis and are not candidates for surgical treatment. Chemotherapy was replaced by more potent drugs directed at the somatostatin receptor (SSR), inhibiting mTOR complex or proangiogenic kinases. Somatostatin analogs are established in the first line therapy. Deciding which drugs to use after the disease progression can be challenging and the treatment approach should be individualized based on each NEN and patient characteristics. The best sequence of treatment can not be defined and biomarkers only slightly support treatment selection, nowadays. Treatment of NENs depends on many factors such as the tumor's type, location, aggressiveness, and hormone-producing capabilities. We discussed treatment options for the gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) from the perspective of current pathomorphological and biochemistry knowledge and based on the evidence generated in pivotal clinical trials. Finally, we reviewed the cardiac safety aspects of agents used to treat GEP-NENs.

NEW PATHOMORPHOLOGICAL CLASSIFICATION AND ITS RELEVANCE FOR THE TREATMENT CHOICE

NENs are heterogeneous malignancies with respect to molecular characteristics and clinical outcome. All they originate from neuroendocrine cells of virtually any organ. However, more than half originate from cells of gastroenteropancreatic (GEP) tract [1]. The diagnosis is based on histopathology, biomarkers and radiology. Grade, evaluated based on the proliferation marker Ki-67 and differentiation determines the clinical aggressiveness of NENs and prognosis. Based on proliferation marker Ki-67 (or mitotic count) neuroendocrine neoplasms are divided into neuroendocrine tumor (NET) G1 (Ki-67 < 3%), NET G2 (Ki-67 3–20%), and neoplasms with Ki-67 > 20%, which are subdivided into well-differentiated G3 NETs (Ki-67 usually between 21 and 55%) and poorly differentiated G3 neuroendocrine carcinomas (NECs) of high malignancy [2]. GEP-NECs are a heterogeneous group of neoplasms classified in different prognostic categories using both tumor morphology (small, intermediate to large cells) and Ki-67 index (must have Ki-67 index > 20%, no lower limit given but usually > 55%) [3, 4]. Well-differentiated tumors have longer survival than poorly differentiated carcinomas [3, 5]. New WHO 2017 classification, combining tumor morphological differentiation and Ki-67 better define prognostic categories. It also has clinical relevance since aggressive, poorly differentiated carcinomas are responsive only to chemotherapy [4, 6, 7].

BIOCHEMICAL MARKERS OF THE DISEASE

GEP-NET origin and location frequently determine its secretory activity and clinical manifestation of functional tumors. The most commonly performed test of GEP-NETs is chromogranin A (CgA) level. CgA is a non-specific marker reflecting secretion aspect of NEN activity. It has limited diagnostic value [8] but can have an importance as a prognostic factor for survival and marker in monitoring the course of the disease and treatment [4, 9, 10]. Some studies identified the correlation between high CgA levels and worse survival. It was suggested that CgA testing might be the preferred method of early detection of recurrence after tumor resection [11]. Elevated baseline CgA concentration exceeding its upper normal value more than tenfold, and its relative increase within the first year of observation were unfavorable predictors of overall survival in patients with pancreatic and midgut neuroendocrine tumors treated with peptide receptor radionuclide therapy (PRRT) [12]. However, none of studies proved that CgA is an independent predictive factor by multivariate analysis. It is a significant limitation of its prognostic value since many other factors than NEN can be responsible for increased serum CgA concentration and considered as confounding factors [4, 13]. Commonly, in clinical trials decrease of CgA level by ≥ 50% is considered as significant effect [13].

The disease manifestation determines the possibility of the use of specific biomarkers. Around one-third of NENs, classified as functioning tumors, produce peptides and hormones. Most commonly serotonin is produced by symptomatic hormonally active forms of NEN of the small intestine, ileum and proximal large intestine. Clinical manifestation of serotonin secretion including flushing, diarrhea, abdominal pain and pulmonary hypertension and right ventricular failure are called carcinoid failure. Cardiac complications occur in about 50% of patients with carcinoid syndrome and are the main cause of death. Thus, their treatment has critical significance for survival. Surgical treatment (replacement of valves) is the only valid form of therapy of carcinoid heart disease nowadays. Screening test for urinary excretion of a serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) has the highest sensitivity in patients with carcinoid syndrome [14]. The choice of other secreted biomarkers depends on the clinical manifestation and type of neoplasm suspected.

SOMATOSTATIN ANALOGS

Somatostatin is a cyclic peptide synthesized in various parts of the digestive system, and also outside it, in the form of a prohormone – preprosomatostatin. Somatostatin working through the receptors has direct inhibitory effects on insulin, glucagon, secretin, GR, thyroid-stimulating hormone (TSH) and gastrin [15]. Most of GEP-NENs express SSRs what allows functional imaging using SSR scintigraphy and targeted treatment. Nowadays, somatostatin analogs play a fundamental role in the treatment of patients with hormonally active NENs. By binding to an SSRs on tumor cells, somatostatin analogs reduce the secretion of biologically active substances, alleviating symptoms of the disease and also inhibit its progress [16].

"Cold" somatostatin analogs

Somatostatin analogs lanreotide and octreotide consist fundaments of effective symptom and tumor growth control. Originally they were developed as anti-secretory agents [17, 18] relieving symptoms of functional NETs, particularly carcinoid tumors but also advanced pancreatic NETs [19]. However, lanreotide and octreotide have never been tested head to head; they seem to offer similar efficacy regarding symptoms control [20]. Their long-acting injectable forms relieved symptoms of carcinoid syndrome in more than 50% of patients and offered the possibility of adjustments doses and injections intervals depending on patient needs [21, 22]. Dose escalation is the first line treatment of the refractory carcinoid syndrome which may lead to complications such as carcinoid heart, mesenteric and retroperitoneal fibrosis, and carcinoid crisis [23]. Even at further symptomatic progression and use of subsequent treatments, somatostatin analogs should be maintained because their discontinuation may worsen carcinoid symptoms [23].

Between the past and current decade, the PROMID and CLARINET studies showed that somatostatin analogs have direct and indirect anti-tumor effects. Direct anti-tumor effects are result of cell cycle arrest and apoptosis, and indirect anti-tumor effects are result of suppression of the secretion of growth factors and angiogenic factors [24]. The PROMID study demonstrated for the first time that octreotide long-acting release (LAR) inhibits tumor growth in patients with advanced functioning and non-functioning neuroendocrine tumors of the midgut or unknown origin [25]. The use of octreotide LAR 30 mg every 4 weeks extended the mean time to tumor progression. After 6 months of therapy, the disease was stabilized in about 67% of cases vs. 53% in placebo group, regardless of the hormonal activity. The median time to progression (TTP) score was 14.3 months compared to 6 months in the control group (tab. 1). The most favorable effect was observed in patients with low hepatic tumor load and resected primary tumor.

The CLARINET study included a broader population of patients than the PROMID study. It included 204 patients with different non-functional NETs G1 and G2 of gastroenteropancreatic or unknown origin. After two-year treatment with lanreotide 120 mg every 4 weeks 65% showed no disease progression compared with 33% of patients treated with placebo. Lanreotide statistically significantly prolonged the median survival time progression free survival (PFS) versus placebo (median PSF was not reached in the treatment group compared to 18 months in the group

TABLE 1.
Summary of approved drugs and pivotal trails for NENs.

Study	Setting	Primary endpoint	Outcome
Octreotide vs. placebo (PROMID) [25]	Midgut or unknown origin NET (non-functioning and functioning)	TTP	14.3 mth vs. 6 mth (HR 0.34; 95% CI 0.20–0.59)
Lanreotide vs. placebo (CLARINET) [26]	Ki-67 < 10% enteropancreatic or unknown origin NET (non-functioning)	PFS	not reached vs. 18 mth (HR 0.47; 95% CI 0.30–0.73)
^{177}Lu-Dotatate and octreotide vs. ^{177}Lu-Dotatate (NETTER-1) [27]	Well-differentiated, metastatic midgut NET	PFS	not reached vs. 8.4 mth (HR 0.21; 95% CI 0.13–0.33)
Everolimus vs. placebo (RADIANT-2) [49]	Progressive, advanced (unresectable or metastatic), well or moderately differentiated NET	PFS	16.4 mth vs. 11.3 mth HR 0.77; 95% CI 0.59–1.00
Everolimus vs. placebo (RADIANT-3) [52]	Progressive disease pancreatic NET	PFS	11 mth vs. 4.6 mth (HR 0.35; 95% CI 0.27–0.45)
Everolimus vs. placebo (RADIANT-4) [53]	Progressive disease lung or GI-NET (non-functioning)	PFS	11 mth vs. 3.9 mth (HR 0.48; 95% CI 0.35–0.67)
Sunitinib vs. placebo [55]	Progressive disease pancreatic NET	PFS	11.4 mth vs. 5.5 mth (HR 0.42; 95% CI 0.26–0.66)
Temozolomide and capecitabine vs. temozolomide (E2211) [48]	Advanced pancreatic NETs	PFS	22.7 mth vs. 14.4 mth (HR 0.58; p = 0.023)

PFS – progression-free survival; HR – hazard ratio; TTP – time to progression

placebo). Effect on elongation of median progression free survival time diseases was observed in patients with hormonally inactive midgut NET G1 and G2 (Ki-67 < 10%) and pancreas, regardless of the volume of liver occupied [26].

Based on the results of the PROMID and CLARINET studies, ENETS stated in their recommendations that somatostatin analogs could be used in stable or progressive disease or in patients with NENs with an undetermined course. Somatostatin analogs are first-line therapy in functionally active NEN including tumors associated with the carcinoid syndrome and functionally active endocrine pancreatic NET. Octreotide LAR is approved for tumor treatment in NET G1 with low hepatic tumor load, whereas lanreotide is approved for enteropancreatic NETs irrespective of hepatic tumor load. Somatostatin analogs can be taken into consideration in low-grade NET and other sites, e.g., lung NETs, when the SSR status is positive, the tumor is slowly growing, and Ki-67 proliferation index is < 10% [7]. Therapy based on somatostatin analog is usually well tolerated and adverse events associated with the first administration disappear within a few weeks [16]. Once started therapy of functional NET should be maintained over subsequent lines of therapy, since disease progression is not an indication to stop symptomatic treatment [4].

"Hot" somatostatin analogs

Peptide receptor radionuclide therapy (PRRT) is a form of radioisotope therapy in which a specially selected peptide having the property of binding cancer cells is combined with a small amount of radioactive material together forming a drug (radiopharmaceutical) called a radiopeptide. The injected radiopeptide moves with the blood to the tumor and joins the tumor cells, delivering a therapeutic dose of radioisotope directly to the tumor cells and limiting the dose of irradiation to normal tissue. PRRT with radiolabeled somatostatin analogs is an option for treatment of metastasized, well/moderate differentiated NETs.

Nowadays, ^{177}Lu-DOTATATE is the most used radiopeptide, due to limited toxicity to kidney and bone marrow [27] comparing to the first radiopeptide used in PRRT, the ^{90}Y-DOTATOC [28]. ^{177}Lu-DOTATATE was studied in the only one phase III randomized trial of PRRT in NEN therapy. The NETTER-1 trial compared ^{177}Lu-DOTATATE plus best supportive care, consisting of octreotide LAR at a dose of 30 mg every 4 weeks to high-dose (60 mg every 4 weeks) octreotide LAR. The study showed an impressive prolongation of progression-free survival (PFS) in patients receiving PRRT compared to patients receiving octreotide LAR. The study was conducted in patients with advanced midgut neuroendocrine tumors (e.g., small bowel, appendix, caecum) who have had disease progression during the first-line somatostatin analog therapy. The median PFS for ^{177}Lu-DOTATATE was 28.4 months, while for octreotide LAR was 8.5 months ($p < 0.0001$) [27] (tab. 1). In the manuscript reporting secondary outcomes of the NETTER-1 data on quality of life benefit was presented. Results showed a clinically and statistically significant delay in the decline of global health, physical and role functioning with ^{177}Lu-DOTATATE compared to high-dose octreotide LAR [29].

Patient inclusion to PRRT therapy is typically based on detectable (≥ Krenning 2) SSR expression but the intensity of radiopharmaceutical uptake does not accurately predict an individual's response. Many other clinical parameters were studied and showed to be prognostic factors of response and survival to PRRT e.g., patient performance status, liver tumor load, biochemical markers and metabolic activity of tumor (based on the FAD grading) [30, 31]. Most recently an algorithm integrating blood-derived NET-specific gene transcripts with tissue Ki-67 values has been developed generating PRRT Predictive Quotient (PPQ). It occurred to be a highly specific predictor of the efficacy of the treatment with an accuracy of 95% [32].

ENETS recommended PRRT after a failure of the first-line therapy. PRRT is a second-line option in midgut NET if the general requirements for PRRT are fulfilled. Extensive hepatic, bone or kidney disease need special consideration and may limit the use of PRRT. PRRT is an alternative to everolimus [33]. The rationale behind the use of everolimus before PRRT is a high incidence of severe toxicity in PRRT-pretreated patients during treatment with everolimus [34].

PRRT have based on the empirical protocols until registration of ^{177}Lu-DOTATATE [35] based on the NETTER-1 trial results. Based on the register protocol treatment in given in fixed dose, in four infusions separated by 8 weeks. This interval can be extended in the case of toxicity. At the day of the PRRT, amino acids infusions are used to protect kidney. It is worth to note that registration of ^{177}Lu-DOTATATE standardized PRRT use, which followed different protocols, adjusting doses to patient weight or body surface and used different number of cycles of treatment (≥ 2 cycles) and intervals between them [30]. The NETTER-1 study showed PRRT could be safely used with somatostatin analogs. Combination of cold and hot somatostatin analogs showed significant clinical benefit over PRRT alone [36]. Combinations of PRRT with other treatments in not yet fully explored. In the literature, there are only a few reports describing outcomes of PRRT in combination with chemotherapy [37, 38]. Other combinations of PRRT are on the early concept stage [39].

CHEMOTHERAPY

Options of chemotherapy include streptozocin (STZ), 5-fluorouracil (5-FU), doxorubicin (DOX) and temozolomide (TEM). Nowadays, role of STZ, 5-FU, and DOX-based regimens is limited due to toxicity and high risk of complications. Chemotherapy has a limited place in well-differentiated NETs. It has a role in the therapy of poorly differentiated and highly aggressive NETs and NECs [4]. As recommended by the ENETS [4, 7], STZ-based chemotherapy is one of the treatment options in pancreatic G1/G2 NETs next to somatostatin analogs and novel targeted drugs. It is preferred regimen in patients with high tumor burden with or without associated clinical symptoms and/or in patients with early tumor progression. In G3 NECs, platinum-based chemotherapy is recommended as the first-line therapy [7].

In recent years temozolomide-based therapy replaces STZ/5-FU regimens, after observation that capecitabine administrated first and followed by temozolomide maximized efficacy of treatment [7]. Use of the combination of capecitabine with temozolomide (CAPTEM) was most commonly reported in patients with pancreatic NETs [40, 41, 42]. It can be considered for high-risk NET of other primary sites [41, 43] and in patients with G3 NETs [44–46]. Use of the CAPTEM in non-pancreatic and G3 NETs is less commonly reported comparing to treatment of pancreatic NETs, and reports in the literature concern from several to few patients. All reposts about CAPTEM use were observational and retrospective studies. Information about CAPTEM efficacy is missing in patients with NECs.

The recent metaanalysis of the CAPTEM use in the pancreatic and non-pancreatic NETs included 15 studies involving 384 patients. The median PFS ranged between 3.4 and 6 months in studies of patients with WHO-graded G3 NENs, and from 12 to 18 months in studies reporting patients with G1/G2 NETs. Median OS was in range from 8 to 83 months [47].

The first two-arms randomized study enrolling patients with advanced low or intermediate grade pancreatic NETs treated with CAPTEM or TEM alone was the E2211 [48]. Median PFS was 22.7 months for CAPTEM vs. 14.4 months for TEM (HR = 0.58; p = 0.023). It is one of the longest PFS reported for pancreatic NET-directed therapy. Nowadays the ENETS does not recommend systemic chemotherapy in non-pancreatic NETs unless G2 NET (Ki-67 > 15%), tumors displaying aggressive progression, or in those which are SSR negative [7].

TARGETED THERAPY

The mechanism of action of targeted medications consists of blocking the function of numerous receptors related to neoangiogenesis and neoplastic cell proliferation and inhibiting metastasis. Targeted therapies are recommended for patients with well-or-moderately-differentiated pancreatic NETs.

Activation of the mammalian target of rapamycin (mTOR) is characteristic for NETs regardless of primary site. Efficacy and safety of everolimus were tested in patients with NETs of different origin in the RADIANT trials including patients active carcinoid tumors (RADIANT-2), with advanced, low-grade or intermediate-grade pancreatic NETs (RADIAN-3) and with progressive NETs of lung and gastrointestinal tract (RADIANT-4).

The RADIANT-2 trial, compared efficacy and safety of the combination of everolimus (10 mg/24 h) plus octreotide LAR with octreotide LAR alone in patients with low-grade or intermediate-grade NETs with carcinoid syndrome [49]. Median PFS was 16.4 months in the everolimus plus octreotide group and 11.3 months in octreotide only group (HR = 0.77; p = 0.026).

The RADIANT-3 study results showed that everolimus delays progression about 1 year in patients with pancreatic NETs. Median progression-free survival was 11.0 months with everolimus as compared with 4.6 months in the placebo group (HR 0.35; p < 0.001) [50]. The overall survival advantage could not be demonstrated in this study since patients for the placebo group, after disease progression, were included into the arm with everolimus. However, achieved in the everolimus group median overall survival was impressive (44 months). The SEQTOR trial assessed which subsequent therapy, STZ or everolimus, results in longer PFS in well differentiated and advanced pancreatic NETs [51]. Results of this study may define optimal sequencing with targeted drugs and chemotherapy in pancreatic NETs.

The RADIANT-4 trial was a phase III study on patients with well/intermediate-differentiated (G1 or G2) advanced non-functional NETs of gastrointestinal or lung origin and with the history of progression in 6 months before enrollment. Patients were assigned to receive everolimus or placebo. Median PFS was 11.0 months in the everolimus group and 3.9 months in the placebo group.

Adverse events of the everolimus include hyperglycemia, cytopenia, rash, diarrhea, oral ulcers, and atypical infections [49, 52, 53]. Results of RADIANT trials allowed introduction of everolimus for the treatment of NETs of different origin: pancreatic, gastrointestinal and lung. Everolimus is registered [54] in the treatment

of progressive disease, but its exact role within the therapeutic sequence remains unclear.

Another agent used in advanced pancreatic NET is sunitinib, an oral inhibitor of tyrosine kinases involved in angiogenesis process. The phase III study compared response rate, PFS, and OS in the sunitinib and placebo groups of patients with low-to-intermediate grade, progressive pancreatic NETs. The study was discontinued early because of a considerable number of deaths in the placebo group and clear benefit of the active treatment. Statistically significant benefit for PFS of 11.4 months in the sunitinib group and 5.5 months in the placebo group (HR 0.42; $p < 0.001$) were reported. Sunitinib improved PFS among patients with a Ki-67 proliferation index of ≤ 5% only with trend toward benefit in patients with Ki-67 > 5% [55]. The most common adverse events of sunitinib were diarrhea, nausea, asthenia, vomiting, and fatigue. Observational data suggest that sunitinib could have similar efficacy in poorly-differentiated pancreatic NETs as in well/intermediate-differentiated tumors [56].

The greatest clinical benefit was observed in those patients who had undergone only cold or hot somatostatin analog therapy before sunitinib treatment. Efficacy and safety of sunitinib did not appear to be affected by such features as the differentiation level of tumor cells, the mass of the pancreatic tumor, the elevated CgA concentration before activating the sunitinib therapy, the expression of SSR, and the functional status of the tumor. The number of treatment trials before did not affect efficacy and safety of the sunitinib. Partial remission was noted in 38% patients and 63% of patients had stabilization of the disease and median PFS was 11 months [57]. The same efficacy and safety irrespective of the types of treatment previously applied is an important advantage of sunitinib, making the angiogenesis inhibitor ease agent in the treatment sequencing. In comparison, caution is needed for patients treated with everolimus in the cases when PRRT was used previously, due to potential toxicity.

Nowadays, sunitinib is considered as effective therapeutic option in patients with progressive non-resectable pancreatic NETs in the second and subsequent lines of treatment, irrespective of the types of treatment previously applied [57].

Everolimus or sunitinib are recommended after failure of SSA treatment, PRRT, or chemotherapy in pancreatic NETs of G1/G2 [58]. They may be considered as the first-line or second-line therapeutic options after chemotherapy, "cold" SSA treatment or "hot" SSA treatment – PRRT in locally advanced, non-surgical or metastatic, well/intermediate-differentiated gastrointestinal NETs [59]. Due to a lack of direct comparative studies available (head-to-head) for these medications, the choice of targeted therapy is based on the medical history of the patient, comorbidities, the side effect profile, and availability of the treatment. The study assessing efficacy of sequential treatment with everolimus and sunitinib in pancreatic NETs showed that median PFS was similar between the everolimus to sunitinib group (36.5 months) and the sunitinib to everolimus group (31.6 months) (HR 0.94; $p = 0.7$) [60].

CARDIAC SAFETY OF TREATMENT

Determining the cardiotoxicity of the drugs described above is quite difficult because the majority of treated patients already have dysfunctions of the cardiovascular system at the start of treatment. Besides, there are no large studies that are assessing cardiac safety in patients with NENs. Safety data concerning somatostatin analogues comes from observations of a patient with acromegaly. Among these patients, nearly 80% had a degree of cardiac valve regurgitation, although none was severe. Incidence did not change over 12 months of somatostatin analog treatment, and most cases of regurgitation were physiologic or mild in severity [61].

Cardiotoxicity of sunitinib is associated development of hypertension, left ventricular ejection fraction decline and congestive heart failure. The most common event (8% of patients) was NYHA class III–IV congestive heart failure. Elevation of blood pressure was noted significant with approximately 47% of patients using sunitinib therapy [62]. The use of everolimus in neuroendocrine tumors therapy may cause cardiac dysfunction. On the basis of analysis of the safety data hypertension was the most common cardiovascular risk factor reported for everolimus. Cardiac diseases associated with everolimus have a spectrum of clinical presentations that range from fatal cases, to reversibly decreased left ventricular ejection fraction. The majority of the cases were confounded by concomitant or prior use of cytotoxic or targeted therapies, or cardiac comorbidities [63]. Patients should receive close monitoring and prompt treatment for individuals who developed hypertension and/or left ventricular ejection fraction decline.

THERAPIES IN DEVELOPMENT

Data on the molecular background of NET is continuously developing to address needs of patients which cannot benefit on the current armamentarium of treatment options. One of such a condition is a refractory carcinoid syndrome, which management is

nowadays restricted to symptomatic strategies or tumor debulking by surgery or PRRT. A monoclonal antibody against vascular endothelial growth factor A, bevacizumab, was tested in the Southwest Oncology Group S0518 trial interferon of alfa-2b with octreotide LAR vs. bevacizumab with octreotide LAR in patients with advanced, poor prognosis carcinoid syndrome. There were no significant differences in PFS between study arms [64]. Another agent, telotristat ethyl, were tested in the TELESTAR trial with patients with carcinoid syndrome with ≥ 4 bowel movements per day on somatostatin analogs. Results showed that treatment with telotrtristat ethyl controlled symptoms and reduced bowel movements frequency by ≥ 30% in 44% of patient [65]. Also, significant reduction in 5-HIAA level was observed: 54.0% and 89.7% for the placebo and for the telotristat ethyl group, respectively. The TELECAST study complemented results of the TELESTRA trial. It was conducted to provide additional safety information. The TELECAST mostly enrolled patients treated with somatostatin analogs for carcinoid syndrome characterized by less severe bowel movement frequency than those patients in the TELESTAR, but also enrolled a smaller number of carcinoid syndrome patients not treated with SSA therapy [65]. Results of both support the safety and efficacy of telotristat ethyl when added to somatostatin analogous in patients with carcinoid syndrome. The most common adverse events of telotristat ethyl were nausea and hepatic enzymes elevation.

Immunotherapy is recent, rapidly emerging therapeutic option for NETs. There is many clinical trials in progress or close to start recruitment that investigate immunotherapy including inhibitors block interactions of programmed death-ligand 1 (PD-L1) in GEP-NETs [66]. There is a correlation between PD-L1 expression with the aggressiveness of high-grade NENs [67]; thus new studies results would be interesting for doctors treating patients with poorly-differentiated NENs. With the results of these studies are associated with high hopes, especially for patients with previous systemic treatment. The end of research is planned for 2019–2020.

CONCLUSIONS

Nowadays there is relatively a wide number of therapeutic options registered and available for patients with GEP-NENs (tab. 1). It generates a challenge to navigate in complex treatment algorithm. Current evidence provides us with insufficient knowledge about right sequences of treatment. Research continues to identify effective and safe sequences of treatments and reliable biomarkers of the disease. It will hopefully result with new efficacious therapeutic regimens with minimal toxicity, which represents an enormous unmet demand in GEP-NEN therapy. Areas of highest disease burden and treatment gaps are refractory carcinoid syndromes and poorly differentiated, high-grade neoplasms treated mainly with chemotherapy. Regarding cardic safety, caution is needed in the case of targeted thrapies. Patients treated with sunitinib or everolimus need to be closely monitored due to potential risk of hypertension and heart failure.

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This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.