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Review

The growing interest in neuroendocrine tumours is due to the dynamic growth of detection of this type of cancer. Neuroendocrine tumours (neuroendocrine neoplasms – NENs / neuroendocrine tumours – NETs) derive from glands, groups of endocrine cells and diffuse neuroendocrine system cells. Mainly they derive from the gastrointestinal tract (gastroenteropancreatic-neuroendocrine tumours – GEP-NETs). Currently the modified WHO classification from 2010 is widely used. An important element in the choice of treatment is histological maturity based on mitotic activity and on assessment of proliferation activity (Ki-67). The treatment of choice is surgery. In most cases, complete surgical removal is impossible because of the advanced staging at the time of diagnosis. In well-differentiated neoplasms where the expression of somatostatin receptors is expected, patients are qualified for somatostatin analogues therapy. Poorly differentiated lesions are qualified for chemotherapy. In the guidelines of ENETS (European Neuroendocrine Tumor Society) from 2007 the rules concerning monitoring depending on the WHO classification were specified.

Key words: neuroendocrine tumours of the gastrointestinal tract and pancreas, therapy, follow-up.

Contemporary methods of therapy and follow-up of neuroendocrine tumours of the gastrointestinal tract and the pancreas

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Introduction

The growing interest in neuroendocrine tumours is due mainly to the dynamic growth of detection of this type of cancer in recent decades. According to their specific nature, they are of interest to several medical specializations and require cooperation between surgeons, oncologists, endocrinologists and nuclear physicians. The disparate nature of this type of cancer often necessitates a variety of approaches to both treatment and follow-up of patients with this disease. Neuroendocrine neoplasms (tumours) (neuroendocrine neoplasms – NENs/ neuroendocrine tumours – NETs) derive from glands, groups of endocrine cells and diffuse neuroendocrine system cells (DES) [1]. In 66% of cases neuroendocrine tumours derive from the gastrointestinal tract (gastroenteropancreatic – GEP, gastrointestinal neuroendocrine tumours – GI-NETs). In the widest currently available epidemiological studies the prevalence reaches 5–8 cases per 100 000 population [2]. Since the introduction of the definition "carcinoid" by Oberndorfer, neuroendocrine neoplasms developing in the digestive tract have commonly been named by this term. The turning point occurred in 2000 when a group of European pathologists introduced a classification under the auspices of the World Health Organization (WHO) which specified the names of these tumours. Currently the modified classification from 2010 is widely used:

- neuroendocrine tumour grade 1 (NET G1),
- neuroendocrine tumour grade 2 (NET G2),
- neuroendocrine cancer, small and large cell type grade 3 (NEC),
- mixed adenoneuroendocrine cancer (MANEC),
- hyperplastic and preneoplastic lesions.

An important element of consideration in the choice of treatment is histological maturity based on mitotic activity of cells in preparations stained with eosin-haematoxylin and assessment of proliferation activity of cells based on immunohistochemical reaction with MIB-1 antibody (anti-Ki-67) [3]. The criteria for histological assessment of maturity are shown in Table 1.

An equally important factor determining the choice of treatment is the clinical stage of disease. In clinical stages I–III there might be possibilities of a cure. In stage IV where we have advanced cancer, only palliative treatment to improve the quality of life can be considered. The treatment of choice is surgery. In most cases, complete surgical removal of the lesion is impossible because of the advanced staging at the time of diagnosis. In the case of a well-differentiated neoplasm with a low proliferative index Ki-67 where the expression of somatostatin receptors (somatostatin receptor scintigraphy) is expected, patients might be qualified for treatment with somatostatin analogues. Poor-

Table 1. The criteria for histological assessment of maturity

Grading	Mitotic activity	Proliferative activity (Ki-67)
G1	< 2	≤ 2
G2	2–20	3–20
G3	> 20	> 20

ly differentiated lesions with a high proliferative index (weak or negligible expression of somatostatin receptors) are qualified for chemotherapy [5,6].

Methods of therapy

Somatostatin analogues

Somatostatin analogues (SA) are now considered as a "gold standard" for the treatment of NETs [6]. These drugs not only reduce the secretion of biologically active substances by abolishing symptoms but also affect the inhibition of disease progression [7]. Therapy with these substances makes use of the fact that about 80% of NETs and their metastases have SSTR2 receptor expression [6, 8, 9]. In clinical practice there are two analogues used: octreotide and lanreotide. They exhibit high affinity for human somatostatin receptors (SRS), type 2 and 5 [10, 11]. Treatment with long acting SA is as effective at suppressing symptoms and tumour progression as short-acting forms that are still used for rapid control of symptoms of functioning NETs [12, 13]. *In vitro* and *in vivo* studies have demonstrated the antiproliferative activity of SA, which may involve direct effects on receptors present on tumour cell membranes, and indirect effects, through inhibition of growth factors and hormones, formation of metastasis, angiogenesis inhibition, induction of apoptosis and effects on lymphocyte proliferation and immunoglobulin synthesis [14, 15]. In 5% of cases of NET reduction in size, and in 40–80% of cases stabilization of tumour growth are observed during SA therapy [12, 16, 17]. Therapy is persistent and associated with administration of Sandostatin LAR 30 mg every 28 days or Somatuline Autogel at doses of 60–120 mg every 28–56 days. These drugs are generally well tolerated and the side effects reported by patients include periodic diarrhoea and abdominal pain, which are often transient. Other side effects are impaired glucose tolerance, and rarely cholelithiasis (in 20–50% of patients) [16].

Isotope treatment of neuroendocrine tumours

In this case, a somatostatin analogue is connected to a radionuclide that is a beta emitter, destroying the cell's DNA structure. Currently the most widely used emitters of ionizing radiation are yttrium (90Y) and lutetium (177Lu) particles [18–23]. In the biggest published study, 90 patients with GEP-NETs were treated with three cycles of radiopharmaceutical (90Y) with activity of a single dose of 4.4 GBq; in no case was complete remission observed, while PR was achieved in 4% of cases and SD in 70%. The median progression-free survival was 16.3 months [24]. These results are comparable to the second largest multicenter phase I study evaluating the therapeutic effect of 90Y-DOTATOC [23]. In clinical use there is also a 90Y-labelled somatostatin analogue [DOTA0, Tyr3] octreotate (DOTATATE), where the C-terminal amino acid threonine is replaced by its alcohol derivative. Changing of the molecular structure has resulted in several times increased susceptibility to the somatostatin receptor 2 (SSTR2) in comparison to DOTATOC [24]. In the preliminary results of the studies using this radiopharmaceutical in GEP-NETs expressing somatostatin receptors, PR was achieved in 37% and SD in 70% of cases.

The first reports of therapy with use of 177Lu-DOTATATE showed promising results: 30% complete (CR) and partial (PR) response, and stable disease (SD) in 40% of cases [25]. These results were confirmed in subsequent studies involving 310 patients with GEP-NET treated with the same substance [26]. Isotope therapy using somatostatin analogues labelled with radioactive isotopes is a promising form of treatment, especially for patients disqualified from surgery and who have demonstrated the existence of somatostatin receptors on the surface of the tumour in receptor scintigraphy. Because of the potentially harmful effect of isotope therapy on renal function, preparations of amino acid mixtures (lysine-arginine) are used, which reduce the absorption of radionuclide [22]. Risk factors that may affect kidney function after radionuclide therapy are the radiation dose used in the various cycles of therapy and cumulative doses of the isotope, patient age and comorbidities such as diabetes and hypertension [27]. Disorders in bone marrow functioning, which, however, are mostly mild and transient, are also observed.

Therapy with ^{131}I-meta-iodobenzyl guanidine

Aside from using ^{131}I-meta-iodobenzyl guanidine (MIBG) scintigraphy in the diagnosis and staging of GEP-NETs, it can be used to select patients likely to benefit from therapy with ^{131}I-MIBG. Visualization of the neoplastic process in scintigraphy is a prerequisite for qualification for this type of therapy. The treatment is carried out for 5 cycles every 3–6 months with 7.4–11.2 GBq doses. Results of studies on use of ^{131}I-MIBG in cases of metastatic disease indicate a 13–15% objective tumour response to therapy. Biochemical response defined as > 50% reduction in the concentration of chromogranin A (CgA) and 5-hydroxyindoleacetic acid (5-HIAA) was estimated at 37–46% [28, 29], but objective tumour response to treatment was estimated at 13–35% [28–30]. Treatment is generally well tolerated, and side effects are similar to those radiopharmaceuticals mentioned above. Therapy using MIBG can be an alternative means of treatment in case of visualization of neoplastic foci in MIBG scintigraphy with no uptake in somatostatin analogue receptor scintigraphy. In patients with an active thyroid gland it is necessary to use liquid iodine or sodium perchlorate to block the uptake of MIBG unbound free iodine.

Chemotherapy

The value of the widely used cytotoxic agents in oncology in cases of neuroendocrine tumours is limited, as evidenced by low rates of objective response and short duration of remission. Combined cytotoxic therapy shows greater efficacy compared to monotherapy. The therapeutic scheme evaluated most often in well-differentiated

neuroendocrine tumours was an association of streptozotocin with doxorubicin and/or fluorouracil. Objective responses are higher (estimated at 30–60%) and longer (10–36 months) compared with the results of monotherapy. The use of multidrug therapy is associated with more frequent and more severe side effects, concerning in particular the combination streptozocin and doxorubicin. In advanced, poorly differentiated NETs platinum derivatives are used. Objective responses were observed in 42–80% of cases when the combination of cisplatin and etoposide was used [31–33] and in 78% of cases with use of oxaliplatin [34]. However, despite the satisfactory results of the treatment response rate, median survival time is between 8 and 11 months [33]. Currently there are considerable difficulties with chemotherapy with streptozotocin due to the limited availability of the drug.

mTOR inhibitors

In two studies carried out recently with the participation of patients with neuroendocrine tumours of the pancreas, there was a promising result of antitumor activity of everolimus (Afinitor) [35, 36]. It inhibits the mammalian target of rapamycin (mTOR), a serine-threonine kinase that stimulates cell growth, proliferation and angiogenesis [35–37]. Autocrine activation of the mTOR signal pathway taking place via the insulin-like growth factor 1 participates in cell proliferation of neuroendocrine pancreatic tumours [38]. In a prospective randomized phase III study using everolimus in 410 patients with advanced low- and middle-grade pancreatic neuroendocrine tumours, significant prolongation of progression-free survival of the disease in the everolimus group compared to placebo was observed [39]. Adverse events were mostly mild, with inflammation of the oral mucosa, rash and diarrhoea most often reported. This drug is registered in Poland for the treatment of unresectable well-differentiated pancreatic neuroendocrine tumours. Research is ongoing to evaluate the efficacy of everolimus in neuroendocrine gastrointestinal tract and lung tumours.

Other medications

Neuroendocrine tumours are characterized by extensive vascularization and high expression of vascular growth factors (VEGF). There are reports of a strong correlation of VEGF expression and tumour size and the ability of tumour metastasis [40]. Currently, there are a number of antiangiogenic agents being evaluated in clinical trials. These include human monoclonal antibody against VEGF (bevacizumab), tyrosine kinase inhibitors (sunitinib, sorafenib, vatalanib, imatinib) and other factors affecting the proliferation of blood vessels, such as thalidomide and endostatins. Among the published results of clinical trials of these drugs, sunitinib has the most promising efficacy. However, this applies only to inoperable pancreatic neuroendocrine tumours. In Poland, none of these preparations have been approved yet for the treatment of GEP-NETs.

Monitoring of treatment

According to the guidelines of ENETS from 2007 [41], the rules concerning monitoring of neuroendocrine tumours, depending on the classification of both the WHO and the TNM and clinical course, were specified.

Endocrine tumours of the stomach

Gastric tumours were divided into five categories:

- benign tumours – benign gastric tumours possible to be removed endoscopically (T1, size less than 1 cm),
- resectable tumours, probably benign – $T_2N_0M_0$ tumours, larger than 1 cm, infiltrating the muscle membrane and submucosa,
- resectable malignant tumours with or without involvement of lymph nodes; this category includes tumours with Ki-67 above 2% (G2 and G3), T2, T3,
- unresectable gastric tumours with or without involvement of lymph nodes and metastases or without metastases G1–G3.

In the case of type 1 (gastritis type A – easily removed endoscopically) monitoring by examination with gastroscopy should be carried out at yearly intervals. Determination of concentrations of gastrin and chromogranin A (CgA) is in this case without clinical relevance. In cases of resective, potentially benign type 2 lesions, the recommended way of monitoring is imaging studies (ultrasound, CT, MRI) after 6 months, followed by repeat testing on an annual basis. Scintigraphy is recommended at the beginning of the disease's detection, then every 2 years. Chromogranin A test should be repeated every 6 months. In the case of type 3 neoplasms, stage G2–G3 imaging studies (ultrasound, CT, MRI) should be repeated every 3 months. In the case of potentially unresectable or diffuse tumours local resection should always be considered as a cytoreductive treatment. Recommendations for monitoring are the same as described above, according to the histopathological evaluation of G1 and G2–G3.

Endocrine tumours of the small intestine

In assessing the progress and effectiveness of treatment of neuroendocrine tumours of the jejunum and ileum secreting serotonin (carcinoid) it is helpful to determine CgA and 5-HIAA concentration. In patients treated with somatostatin analogues a decrease in urinary 5-HIAA and blood CgA levels coexists with a reduction in the intensity and frequency of clinical symptoms (flush, diarrhoea). There is good agreement (80%) between the change in tumour size and the change in CgA levels. Even greater compliance (88%) was found in patients with non-functioning tumours, where it is not possible to use another marker [42–44]. Imaging studies (ultrasound, CT) should be carried out every 6 months. In patients with carcinoid heart syndrome echocardiography also should be repeated every 6 months. In case of progressive disease control imaging and biochemical studies should be performed every 3 months [45–47]. Monitoring of patients with GEP/NET of the small intestine should be for life. Epidemiological data indicate that 25 years after diagnosis, only 25% met the criteria for cure [48].

Endocrine tumours of the appendix

In assessing the progress and effectiveness of treatment of patients with NET of the appendix it may be useful to mark

CgA and 5-HIAA [46], although the authors of the ENETS recommendations from 2009 stated that markers should be measured in case of positive imaging studies [43]. In the case of non-metastatic NET of the appendix with a diameter of less than 2 cm (T1, T2), considered as cured after resection of appendicitis or hemicolectomy, the determination of CgA concentration should be done once 6–12 months later. In the case of functioning tumour the determination of urinal 5-HIAA concentration should be performed. In addition, all patients after surgery should have imaging studies (ultrasound, CT, MRI) performed after 6 and 12 months. Somatostatin receptor scintigraphy should be performed every 2 years for G1 tumours, and every year in the case of G2 and G3 tumours [49].

Neuroendocrine tumours of the colon

After endoscopic or surgical treatment of lesions with size up to 1 cm, without lymph node metastases, monitoring of patients is not recommended. If tumours exceed 2 cm, control tests should always be planned, even if the surgery was radical. For tumours measuring 1–2 cm a control test should be proposed in case of high-risk features (presence of angioinvasion, infiltration of the proper muscle membrane, high mitotic index) [50]. The monitoring methods are colonoscopy, CT, MRI and CgA [51].

In patients with high risk positive markers, research should be carried out every 4-6 months in the first year, and then every year for 10 years, and in patients without markers of high risk, once a year for 10 years [52].

Pancreatic neuroendocrine tumours

Monitoring of treatment includes clinical examination as well as biochemical and radiological assessment and it should be tailored to the severity of the disease, to demonstrate the results of surgical treatment and also to reveal indications for additional therapy. Cases of well-differentiated pancreatic endocrine tumours should have a control test carried out every 6–12 months (endoscopic ultrasound, CT, MRI, insulin, gastrin, CgA). Somatostatin receptor scintigraphy or PET-Ga68 should be performed 6 months after surgery. In patients with poorly differentiated tumours, imaging studies should be performed every 2–3 months [53, 54].

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