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Gastro-entero-pancreatic neuroendocrine tumors – a challenging group of rare neoplasms

Guzy neuroendokrynne układu pokarmowego – wyzwanie terapeutyczne rzadkich nowotworów

Summary
Gastro-entero-pancreatic neuroendocrine tumors (GEP – NETs) are a heterogenous group of rare neoplsms which may develop from neuroendocrine cells located in different parts of the digestive system (the foregut, the midgut and the hindgut). The classification is based on the mitotic rate and Ki67 labeling index. Therapy of GEP-NETs consists of different oncological methods such as: surgery, somatostatin analogs, interferon alpha, radioisotope therapy, chemotherapy and targeted therapy. Surgery remains the standard of care of neuroendocrine tumors of the digestive system. Resection or palliative debulking of liver metasatses may improve overall survival. Somatostatin analogs are not only used in controlling hormonal symptoms in patients with functional GEP-NETs but also as antiproliferative agents. Peptide receptor radionuclide therapy is a special form of therapy in which somatostatin analogs are conjugated with isotopes. Chemotherapy is of limited value in well-differentiated GEP-NETs but is recommended in poorly differentiated GEP-NETs. Also, chemotherapy should be considered in individual patients when there is evidence of failure with other therapies. Targeted therapy is a new approach in the treatment of pancreatic neuroendocrine tumors.

Key words: gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs), somatostatin analogs, interferon, targeted therapy, sunitinib, everolimus, chemotherapy, peptide receptor radionuclide therapy (PRRT), surgery

Streszczenie
Guzy neuroendokrynne układu pokarmowego stanowią heterogenna grupę rzadkich nowotworów wywodzących się z komórek neuroendokrynnych zlokalizowanych w różnych częściach układu pokarmowego (przedniej, środkowej i tylnej częsci prajelita). Klasyfikacja tych nowotworów oparta jest na indeksach: mitotycznym i Ki-67. Terapia guzów neuroendokrynnych układu pokarmowego opiera się na różnych metodach: leczeniu chirurgicznym, stosowaniu: analogów somatostatyny, interferonu alfa, terapii radioizotopowej, chemioterapii i terapii ukierunkowanej molekularnie (terapii wcelowanej). Chirurgia jest podstawową metodą leczenia. Resekcja lub zabiegi cytoredukcyjne zmian przerzutowych w wątrobie mogą przedłużać całkowity czas przeżycia. Analogi somatostatyny są stosowane nie tylko w opanowaniu objawów hormonalnych występujących w zespole rakowiaka , lecz także jako leki o działaniu antyproliferacyjnym. Terapia radioizotopowa wykorzystuje analogi somatostatyny sprzężone z izotopami. Chemioterapia ma ograniczone zastosowanie w terapii guzów neuroendokrynnych układu pokarmowego, ale jest rekomendowana w nisko zróżnicowanych nowotworach

lub w przypadku niepowodzenia innych terapii pierwszego rzutu. Terapia ukierunkowana molekularnie jest nowym podejściem terapeutycznym w leczeniu guzów neuroendokrynnych trzustki.

Słowa kluczowe: guzy neuroendokrynne układu pokarmowego, analogi somatostatyny, interferon, terapia ukierunkowana molekularnie (terapia celowana), sunitynib, ewerolimus, chemioterapia, terapia radioizotopowa, chirurgia

Gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs) are a heteterogenous group of rare neoplasms that present many clinical challenges. It includes both malignant and rather benign variants of neoplasms. Although the majority of GEP-NETs are sporadic, there are some inherited syndromes connected with these neoplsms such as: multiple neoplasia type 1 and 2 (MEN-1 and MEN-2), von Hippel-Lindau syndrome, tuberosclerosis and neurofibromatosis syndrome. The incidence of these tumors keeps increasing. For example the database of the National Cancer Institute demonstrated that the age-related incidence of neuroendocrine neoplasms (NEN) increased 481% within 30 years, from 1.09/100,000 in 1973 to 5,25/100,000 in 2004 (Yao JC et al ,2008) and the incidence of gastroenteropancreatic tumors increased 365% within 30 years, from 1,00/100,000 in 1973-1977 to 3,65/100,000 in 2003-2007 (Lawrence B, 2011). This type of tumors may develop from neuroendocrine cells located in different parts of the body and are grouped according to their embryonic origin: the foregut (lungs, thymus, stomach and duodenum), the midgut (jejunum, ileum, appendix, and the proximal part of large bowel), and the hindgut (distal part of large bowel and rectum). These rare tumors are generally characterized by a relatively indolent clinical course but the optimal management still remains to be defined.

Although there are different classifications of GEP-NET tumors such as: World Health Organization (WHO), American Joint Committee on Cancer (AJCC), North American Neuroendocrine Tumor Society (NANETS) the most commonly accepted are the classification of European Neuroendocrine Tumor Society (ENETS) and WHO . The both classifications include:

- NET – neuroendocrine tumor grade 1 (G1) – high grade of differentiation
- NET – neuroendocrine tumor grade 2 (G2) – intermediate grade of differentiation
- NEC – neuroendocrine carcinoma grade 3, large cell or small cell
- MANEC – mixed adenoneuroendocrine carcinoma

Both classifications calculate the tumor proliferation either on mitotic rate or Ki-67 labeling index. That is why the grading is based on these both parameters. Mitotic rate is expressed as the number in 10 high power microscope fields (hpf) or by percentage of cells labeling by immunohistochemistry for Ki67. The Ki67 labeling index usually correlates well with mitotic rate. The grade of GEP-NETs is a fundamental predictor of clinical outcome. For GEP-NETs a mitotic rate below 2/10 hpfs and Ki67 index <3% are typical for low grade malignancy (G1 – high grade of differentiation) and separate this type of tumors from tumors with intermediate grade of differentiation (2-20/hpfs and Ki67 index 3% - 20%), while poorly differentiated GEP-NETs (G3 grade) are characterized by a mitotic rate > 20/10 hpfs and Ki67 index >20%.

Therapy of GEP-NET tumors consists of different oncological methods such as: surgery, chemotherapy, radioisotope therapy, hormonal and targeted therapy.

Complete surgical resection of GEP-NET tumors is considered as the only potentially curative treatment. As far as non-functioning pancreatic neuroendocrine tumors are concerned, aggressive surgery is recommended for localized tumor larger than 2 cm (Hellman P et al, 2000; Triponez F et al, 2006) and lymph node dissection for tumors of 2.5 cm or larger and at least node sampling for tumors with a diameter of 1 cm or more. Debulking surgery should be advised in advanced tumors (Kim MJ et al, 2012). Resection of primary tumor in the setting of metastases may improve overall survival, especially in patients with small bowel tumors (Givi B et al, 2006; Schurr PG et al, 2007). Resection or palliative debulking of liver metastases in carefully selected patients may improve overall survival as well as control hormone mediated symptoms. However, such an approach is connected with a high recurrence rate up to 99% at 10 years (Mayo SC et al, 2010). Saxena et al. in a systematic review of clinical studies done before September 2010 confirmed that hepatic resection for hepatic metastases in GEP-NETs provides symptomatic benefit and is associated with favourable survival outcome although the majority of patients develop disease progression (Saxena A, et al., 2012). The other regional therapies for GEP-NETs include : hepatic arterial embolization, hepatic arterial chemoembolization, radiation therapy with 90Y-labeled microspheres. Although these treatments are relatively well-tolerated with good radiographics response rates > 50%, there are no randomized trials supporting these beneficial results (Bergsland EK, 2013).

Somatostatin analogs (SA) play an important role in the treatment of GEP-NETs. They are not only used in controlling hormonal symptoms of patients with functional GEP-NETs but also as antiproliferative agents. SA control more than 70% of patients with carcinoid syndrome. They inhibit the secretion of peptides from tumors through somatostatin receptor subtype 2 (SSTR-2) and 5 (SSTR-5) . After activation of these both receptors intracellular potasium and calcium channels are activated , which leads to reduction of intracellular calcium and inhibition of protein kinase A through level inhibition of cyclic adenosine monophosphate (Toumpanakis C, Caplin ME, 2013). The antiproliferative activity of SA was shown in retrospective and in a prospective randomized phase III trial (PROMID study). In retrospective studies partial response (PR) was observed in up to 10% of paietnts and stabilization (SD) in about 50% of patients. In patients with progressive disease treatment with SA resulted in lower percentage of PR (3% - 7%) and SD (28% - 57%). Two recent studies (Bianchi A et al, 2011; Massuti B et al, 2011) demonstrated that treatment with lanreotide autogel led to higher percentage of SD (65,3% and 88,9%, respectively).

The PROMID trial demonstrated that progression-free survival (PFS) in patients with midgut GEP-NETs receiving octreotide LAR (long - acting release) was more than twice as long compared to patients who received placebo (14.3 months versus 6 months, retrospectively) (Rinke A et al., 2009). The antiproliferative activity of SA is based on direct and indirect mechanisms. The direct mechanism is connected with binding of SA to SSTR-2 and SSTR-5, which leads to inhibition of mitosos and cell cycle arrest. The indirect antiproliferative activity is mediated by:1) decreased production of several growth factors such as growth hormone and epidermal growth factor, 2) inhibition of angiogen-

esis, 3) immunomodulation through activation of natural killer cells (Toumpanakis C, Caplin ME, 2013). The final results of a phase III trial (CLARINET study) investigating the role of another SA analog , lanreotide LAR (long – acting release), are expected to be published soon.

A special form of SA therapy is peptide receptor radionuclide therapy (PRRT) based on yttrium-90 and lutetium-177 isotopes conjugated with SA. Radiopeptides bind to SSTR-2 and are internalized, which allows delivery of radioactivity to tumor and adjacent tumor cells.The study of Kwekkebbom et al. showed high percentage of complete and partial responses (30%) and stabilization (41%) (Kwekkebbom DJ et al., 2003). PRRT is recommended after failure of other medical therapies but the role of this therapy requires further elucidation in randomized trials. Such a trial comparing treatment with PRRT with high dose octreotide LAR is currently underway.

Intereferon alpha (IFNα) is another biological therapy used in GEP-NETs. IFNα binds to a common receptor at the surface of tumor cells via induction of the JAK-STAT pathway, which leads to initiation of transcription of interferon inducible genes. There are two recommendations for using INFα in GEP-NETs. Firstly, IFNα is considered as a standard treatment for carcinoid syndrome. Secondly, IFNα is frequently used as asecond-line therapy if somatostatin analogs are not tolerated or patients are refractory to these drugs. Stabilization is observed in 50% - 60% of patients treated with IFNα and symptopms of carcinoid syndrome are controlled in 40% - 70% of the patients. However, treatment with IFNα is connected with high toxicity including: influenza-like symptoms, fatigue and weight loss.

Chemotherapy is another metod of treatment of neuroendocrine tumors of digestive tract. However, the role of chemotherapy is different in well differentiated and in poorly differentiated GEP-NETs. Chemotherapy is of limited value in GEP-NETs with low proliferation indices but may be useful in higher grade tumors. Objective responses range between 0% - 33% for drugs including 5-fluorouracil, streptozocin and dacarbazine when used in monotherapy or in combination. There are inconsistencies between clinical studies with respect to responses, rate of criteria, especially those comparing the role of 5-fluorouracil and doxorubicin versus streptozocin and 5-fluorouracil. However, the percentage of responses in well differentiated GEP-NETs is low and this therapy is associated with high toxicity. That is why the chemotherapy is not recommended in well differentiated GEP-NETs. The aggressiveness of poorly differentiated GEP-NETs is similar to that of small cell lung cancer. That is why is such tumors the treatment consists of palliative chemotherapy and corresponds to the treatment of extensive stage small cell lung cancer (Olsen et al., 2012). Survival outcomes are unaffected by the Ki67 in contrast to well-differentiated GEP-NETs tumors where such association was shown (Binderup et al., 2010). Generally chemotherapies based on cisplatin and etoposide or three drug regimen including carboplatin, etoposide, and vincristine are used. The median survival in first regimen is 19 months , while in the second one is 15.3 months (Olsen et al., 2012). Well differentiated GEP-Nets usually did not respond to chemotherapy based on cisplatin and etoposide (Moertel et al., 1991). Chemotherapy should be also considered in individual patients when there is evidence of failure with other therapies such as somatostatin analogs, interferon or PRRT in the absence of alternative antiporoliferative drugs.

Targeted therapy is a new approach in the treatment of GEP-NET tumors. The rationale for using such a therapy lies in good vascularization of these tumors and in dysfunction of mTOR pathway in tumors located in the pancreas. Of special interest is sunitinib, an inhibitor of VEGF *(vascular endothelial growth factor)* and PDGF (*platelet-derived growth factor* receptors. It was investigated in many studies. In a double-blind placebo-controlled phase III study of Raymond et al. treatment with sunitinib was associated with an improvement in median PFS from 5.5 to 11.4 months compared with placebo (Raymond E et al, 2011). Everolimus , an oral inhibitor of mTOR, was investigated in a multinational double-blind placebo-controlled phase III study in patients with pancreatic NET (RADIANT-3 study). Everolimus significantly prolonged median PFS from 4.6 to 11 months compared with placebo (Yao JC et al.,2011). However, beneficial results of antiangiogenic agents and mTOR inhibitors are limited by the development of resistance. That is why new strategies are tested such as targeting multiple proangiogenic pathways or targeting VEGF with transcription factors (hypoxia-inducible factor 1) and everolimus with combination therapy with cixutumumab (a monoclonal antibody) or somatostatin analogues: octreotide and pasireotide ((Dang M et al., 2012).

Conclusions

1. GEP-NETs tumors are a challenging group of rare neoplasms.
2. Surgery still remains the gold standard of treatment of these tumors
3. Somatostatin analogs may be used in controlling hormonal symptoms of patients with functional GEP-NEWTs as well as antiproliferative agents
4. The role of peptide receptor radionuclide therapy requires further elucidatrion in randomized trials
5. Chemotherapy is of limited value in well-differentiated GEP-NETs while is recommended in poorly-differentiated GEP-NETs. Also, chemotherapy may be used as a second line treatment after failure of other therapies
6. Targeted therapy is a new approach in the treatment of pancreatic neuroendocrine tumors.

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