NEUROENDOCRINE TUMOURS: 2016 UPDATE

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Abstract: *The field of neuroendocrine tumours (NETs) is complex and dynamic, recently becoming a hot spot on publications area. We aim at presenting new frames of NETs approach. This is a narrative review using an English literature PubMed research (publications only from 2016). The main stream of NETs management includes somatostatin analogs with good effects on carcinoid syndrome and proliferation rate; peptide receptor radionuclide therapy (NETTER-1 study). New products as peripheral tryptophan hydroxylase oral inhibitors (TELESTAR study) are opening promising doors. RADIANT-4 results were recently published; everolimus becoming an essential line therapy especially for pancreas. Surgical approach of NETs remains important. The decision of surgery is based on tumours' size and site, functional pattern, local and distant invasion. The indications of performing surgery for metastasis are mostly unchanged and this decision must be taken under multi-disciplinary considerations. Despite recent progress, there are still many missing pieces of the puzzle represented by NETs domain.*

INTRODUCTION

The field of neuroendocrine tumours (NETs) is complex and dynamic, recently becoming a hot spot on publications area.(1,2,3) The prevalence is higher due to various triggers and increased awareness, so early detection is provided and, potentially, due to modern management which might increase survival.(1,2,3) For instance, digestive NETs got an incidence of 2.39/100.000 people/year and a prevalence of 35/100.000 people/year.(1) NETs behaviour depends on site, patients' age, morbidities, endocrine functionality and genetic background.(2) The large heterogeneity impacts their management.(1,2)

New options as telotristat etiprate (a serotonin inhibitor) are developing for carcinoid syndrome.(2)

Progresses have been made in signalling pathways involved in NETs growing, for example, Notch signalling, even complex, is related to either tumorigenesis or tumour suppression while RAF/MEK/ERK pathway, despite being described in normal and cancerous cells, is connected to mutations found in lung cancers.(4,5) Further understanding of best diagnostic tools and management is still necessary despite obvious advance.(1,3,6)

PURPOSE

We aim to present new frames of NETs approach.

MATERIALS AND METHODS

This is a narrative review using an English literature PubMed research (publications from 2016). We focus on specific NETs sites and assessment, endocrine and genetic point of view etc.

RESULTS

Specific types of NETs. Data reported or reviewed in 2016 refers to localizations or classes. Well-differentiated carcinomas according to 2010 WHO criteria (grade 3 NETs) have a more aggressive behaviour if Ki67>20% with a distinctive new category of pathological report (called well-differentiated grade 3 NET).(7) This sub-type, which is not rare, is found in pancreas, colon and controversies are related to the best management: surgery is followed by chemotherapy.(7) Well- and intermediate- differentiated lung NETs have non-specific presentations and variable history, thus they may be missed.(8) Everolimus is the most important therapy, a part from surgery, regardless carcinoid syndrome.(8)

The classification of lung malignancies is less adapted for their growing and function (typical and atypical carcinoid, small cell carcinoma, large cell neuroendocrine carcinoma etc) and re-structuring is needed.(9) Regarding digestive NET's, in 2016, Babu et al. referred to a less described entity: esophagus NETs which are frequent within the sixth decade, with a male to female ratio of 1.5, particularly located on the lower third part up to the stomach.(10) Rectal NETs have an increase of the prevalence due to endoscopy performed during screening protocols (an incidence of 1/100.000 people/year; 90% of < 1 cm due to early detection).(11) Cloyd et al. analyzed cystic pancreatic NETs: cyst component associates a better prognosis; pure cysts may be initially followed due to good prognosis.(12) Cystic lesions of the pancreas are easier detected now including primary health care.(13)

Another less described group includes mixed tumours, with at least 30% of cells of NETs type, respective non-NET type (like epithelial); controversies are: cut-offs not unanimously accepted; their clinical features and prognosis since every organ may be affected of such tumour; WHO classification includes exclusively digestive adenoneuroendocrine carcinomas, while other sites lack a specific terminology and La Rosa et al. proposed the term of

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"MiNEN (mixed neuroendocrine-nonneuroendocrine neoplasm)".(14)

NETs assessment. The tests for NETs confirmation, staging and grading are various. Neoplasm- produced biomarkers are non-invasive and useful in screening and prognosis.(15)

Continuous seeking for tumour knowledge extended to biochemical amines assays at blood and biological samples (especially for carcinoid syndrome).(15) Traditional imagery are reinterpreted as diffusion-weighted Magnetic Resonance Imagery for hepatic metastases, which remains a rapidly proving results method.(16) PET (Positron Emission Tomography), using 18F-FDG or 68-Ga is essential together with pathological report offering the best staging for individual therapeutically strategy.(17) SPECT/CT (single photon emission computed tomography/computed tomography) using (99m)Tc (technetium)- labelled somatostatin receptor analogues has the advantage of functional anatomy assessment with 3D volume acquisition with higher accuracy.(18)

Advanced methods of diagnosis also provide therapy. Endoscopic ultrasound is used for small, otherwise hardly detectable gastro-entero-pancreatic NETs and high frequency miniprobes are used for identification, biopsy and removal.(19) Devices for implantable microspheres are able to deliver intra-arterial radionuclides (like Ytrium-90) into hepatic arteries thus increased targeted radiation exposure directly to liver NETs avoiding the damage of external radiation.(20)

Genetic point of view. New data are provided on NETs- associated genetic background. Carcinoid tumours of the small intestine have been linked with loss of chromosome 18 in 60-90% of cases and potentially with 18zq21 mutation and epigenetic abnormal regulation.(21) One out of five NETs underlines a genetic anomaly; including multiple endocrine neoplasia syndromes but other 24 gene disturbances have been described up to this moment.(22,23)

Knowing genetic implications is essential for each patient even the same person may display a large heterogeneity into the same tumour.(24) Overall, many aspects are still incompletely known.

Endocrine point of view. Ectopic endocrine production has been found like growth hormone secreting lung NETs with paraneoplasic full blown picture of acromegaly.(25) Adrenocorticotropic hormone is expressed by NETs at imunohistochemistry, biochemistry and clinical level; pulmonary and mediastinal tumours display a particular risk.(26) A first case of such profile with intracranial NETs has been published by Liu H et al.(27) Chromogranin A, gastrin and pancreatic polypeptide still have a great utility in pancreatic NETs but mostly for sporadic forms and poorly for multiple endocrine neoplasia type 1.(28)

Li Y et al. focused on familial hyperparathyroidism which is found in hyperparathyroidism-jaw tumour syndrome, and type 1 and 2 multiple endocrine neoplasia accounting for 2-5% of all cases.(29) NETs for these three circumstances are: parathyroid carcinoma; pancreatic, thymus and lung NETs; respective medullar thyroid cancer and pheocromocytoma.(29) Large trials are still considered deficient in this area.

We also mention some papers referring to atypical and exceptional locations of NETs. Two cases of thyroid paragangliomas have been described by Pelizzo et al, noting the fact that first case was published by Van Miert in 1964 and 50 cases have already been reported in literature.(30) A link with gynaecological endocrinology is seen in cases with synchronous NETs of classical locations and androgen producing ovarian neoplasia, probably sharing genetic backgrounds.(31) Two women with schwannomas of genitalia have been reported by Jiang et al., reviewing 64 previous similar cases.(32)

Therapeutic approach. The main stream of NETs management includes somatostatin analogs with good effects on carcinoid syndrome and proliferation rate (as previously shown studies as PROMID, CLARINET); mTOR inhibitors as everolimus (RADIANT studies); peptide receptor radionuclide therapy (NETTER-1 study).(33,34,35) New products as peripheral tryptophan hydroxylase oral inhibitors (TELESTAR study) are opening promising doors.(33,34,35) RADIANT-4 results were recently published; everolimus becoming an essential line of NETs.(36,37) Snitinib showed its effectiveness for pancreatic NETs.(38) Chemotherapy is useful in advanced NETs as capecitabine, gemcitabine, temozolamide etc.(39,40) A meta-analysis provided by Wong at al. showed that standard streptozotocin plus 5-fluorouracil has similar response rate with other chemotherapies while interferon may be superior but with similar survival. Its risk of hematological events is higher while risk of renal damage is lower.(41)

Surgical approach of NETs remains important.(33,34,42) The decision is based on tumours' size, site, functionality, mass effects, invasion.(42,43) Its indications for metastasis are mostly unchanged and this decision must be taken under multi-disciplinary considerations.(44) Selected cases may skip classical surgery like stomach NETs treated with endoscopic resection for small low-risk lesions.(45) Receptor- based radioimmunotherapy is a challenging domain and somatostatin analogues may be labelled with radioactive markers as (111)In, (177)Lu, (90)Y.(33,46)

DISCUSSIONS

A special field is represented by the introduction of guidelines for clinical practice; mention European Society of Endocrinology (ESE) via European Network for the Study of Adrenal Tumours (ENS@T) published in 2016 for post-operative pheocromocytoma/paraganglioma.

Surgery remains the first line for both conditions. Patients with paragangliomas need genetic tests, yearly endocrine follow-up for 10 years after surgery except for young patients, those with aggressive forms and/or positive genetic mutations who need lifelong check-up.

CONCLUSIONS

Despite recent progress, there are still many missing pieces of this challenging puzzle represented by NETs domain.

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