New Trends in Treatment of neuroendocrine Tumors

Essay

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By

Kareem Mohammed Khaled

M.B.B.Ch

Under Supervision of

Prof. Dr. Atef Youssef Ryad

Professor of Clinical Oncology and Nuclear Medicine
Faculty of Medicine – Ain Shams University

Prof. Dr. Amr Lotfy Farag

Assistant Professor of Clinical Oncology and Nuclear Medicine
Faculty of Medicine – Ain Shams University

Dr. Dalia Abd El Ghany El khodery

Lecturer of Clinical Oncology and Nuclear Medicine
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
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Kareem Khaled

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List of Abbreviations

Abb.	Meaning
5-HIAA	Hydroxyindoleacetic 5 acid
ACTH	Adrenocorticotrophic hormone
CgA	Chromogranin
DFS	disease-free survival
DTPA	with diethylene-triamine-pentaacetic acid
EC	enterochromaffin cells
EGFR	epidermal growth factor receptor
ENETS	europian neuroendocrine tumor society
ESCC or EPSCC	Extrapulmonary small cell carcinomas
GEP-NETs	gastroenteropancreatic NETs
GERD	gastroesophageal reflux disease
HAE	hepatic arterial embolization
hCG	human chorionic gonadotrophin
HIF	*Hypoxia-inducible factors*
HPFs	high-power fields
HRQoL	health-related quality of life
LDCVs	large-dense-core vesicles
MEN1	multiple endocrine neoplasia 1
MIBG	metaiodobenzylguanidine
NETs	Neuroendocrine tumors
NF1	neurofibromatosis
NSE	Neuron-specific enolase
OS	overall survival
PDGFRs	platelet-derived growth factor receptors
pNETs	panceriatic NETs
PP	pancreatic polypeptide

Abb.	Meaning
PRRT	Peptide receptor radionuclide therapy
PUD	peptic ulcer disease
RCT	randomized control trial
RECIST	Response Evaluation Criteria in Solid Tumours
RFTs	Rare functioning tumors
SD	stable disease
SEER	Surveillance Epidemiology and End Results
SIRT	Selective internal radiotherapy
SPECT	single photon emission computed tomography
SRS	Somatostatin receptor scintigraphy
SRS	Somatostatin receptor scintigraphy
SSLVs	small synaptic-like vesicles
sstr	Somatostatin receptors
Syn	Synaptophysin
TSC	tuberous sclerosis
UKINETS	The UK and Ireland Neuroendocrine Tumor Society
VEGF	Vascular endothelial growth factor
VHL	von Hippel–Lindau
VIP	vasoactive intestinal peptide
VMAT1	vesicular monoamine transporter 1
WDHA syndrome	watery diarrheahypokalemiaachlorhydria
WHO	The World Health Organization
YSR	year overall survival rates
ZES	Zollinger-Ellison syndrome

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Introduction

Neuroendocrine tumors (NETs) consist of a diverse groups of tumors composed of cells showing neuroendocrine cell differentiation (secretory granules), a subset of which can be further classified by their dominant secretory products ***(Barker et al., 2007).***

Neuroendocrine are ‘rare’ tumors with a relatively low incidence (5/100,000 population), and high prevalence, higher than any other upper gastrointestinal cancer ***(Yao et al., 2008).***

Over 90% of NETs are sporadic, the remaining10% are associated with familial syndromes including multiple endocrine neoplasia 1 (MEN1) syndrome, von Hippel-Lindau (VHL), tuberous sclerosis (TSC) and neurofibromatosis (NF1) ***(Calendar, 2006).***

Current pathological staging and grading differs between Europe and the USA; however, both the classification systems are centred around the primary site of the tumor and histological grade ***(Kulke et al., 2011).***

Nuclear medicine plays a vital role in the imaging and treatment of neuroendocrine tumors (NETs). Somatostatin receptor scintigraphy (SRS) with [111In-DTPA] octreotide has proven its role in the diagnosis and staging of gastroenteropancreatic NETs (GEP-NETs) ***(Jaap et al., 2011).***

Surgical resection is the only curative treatment for NETs. However, few cases are detected early enough to avoid residual disease or liver metastases. Surgery may also be considered in a palliative setting by way of debulking for alleviation of pressure and hormonal or obstructive symptoms ***(Norlen et al., 2010).***

Somatostatin analogs are often used as long-term preparations injected monthly. A recently completed placebo-controlled double-blind study proved the tumor proliferation inhibiting effect of somatostatinanalogs ***(Rinke et al., 2009).***

The choice of chemotherapy regime depends on the grade (based on Ki-67 proliferative index), primary site of the tumor and stage of disease. Combination chemotherapy with up to three drugs including streptozocin, doxorubicin, 5-FU (or capecitabine), temozolomide, cisplatin and etoposide is commonly used, the exact schedule and dosing varies from centre to centre ***(Pavel et al., 2011).***

Radiotherapy is an effective modality for achieving local control in patients with panceriatic NETs (pNETs). Radiotherapy produces high rates of symptomatic palliation and freedom from local progression. Prospective trials of radiotherapy for (pNETs) are warranted **(*Joseph et al., 2009)***.

It is well documented that NETs are highly vascularised, and immunohistochemistry studies demonstrate that Vascular endothelial growth factor (VEGF) and Hypoxia-inducible factors HIF activation markers are over-expressed in panceriatic NETs (pNETs) ***(Pape et al., 2011).***

Initial clinical trials investigating anti-VEGF-related therapy included the use of sorafenib and bevacizumab. More recently, sunitinib has demonstrated improved progression free survival (PFS) in a large phase III RCT when used selectively in pNETs ***(Raymond et al., 2011).***

The molecularly targeted therapies everolimus and sunitinib have been rationally and successfully applied to the treatment of low–intermediate-grade pNETs. Everolimus was shown to improve progression-free survival by 6.4 months in pNET and 5.1 months in patients with carcinoid syndrome (including gastrointestinal and bronchial NETs) ***(Anna et al., 2012).***

The UK and Ireland Neuroendocrine Tumor Society (UKINETS) guidelines for the management of GEP NETs state that sunitinib or everolimus may be used as a line of therapy for patients with advanced(inoperable or metastatic) progressive (radiological evidence of disease progression within 12 months), well-differentiated pNETs ***(Ramage et al., 2012).***

Aim of the Work

The aim of this work is to review the updates of national and international researches regarding the new trends in management of neuroendocrine tumors.

Epidemiology

Neuroendocrine tumors are ‘rare’ tumors with a relatively low incidence (5/100,000 population), and high prevalence, higher than any other upper gastrointestinal cancer ***(Yao et al., 2008).***

The incidence for small intestinal neuroendocrine tumor (NETs) (carcinoids) is estimated to be from 0.32/100 000/year (England) to 1.12/ 100 000/year (Sweden). The incidence for rectal tumors is 0.86/ 100 000/year, for pancreatic 0.32/100 000/year and for gastric NETs 0.30/100 000/year ***(Oberg et al., 2013).***

The prevalence of pheochromocytoma and paraganglioma can be estimated to lie between 1:6500 and 1:2500, with the annual incidence in the United States of 500 to 1600 cases per year ***(Herbert et al., 2010).***

The estimated incidence of (p-NETs) in Europe and the USA is <1 per 100,000 individuals per year; however, the number of PanNETs diagnosed has increased considerably over the past four decades ***(Halfdanarson et al., 2008).***

Thorough necropsy studies of many individuals have demonstrated gastrointestinal neuroendocrine tumors to be far commoner than expected from the number of tumors identified in living patients ***(Kimura et al., 1991).***

The most frequent sites of NETs are the gastrointestinal tract (70%) and the broncopulmonary system (25%); the distribution of tumors inside the gastrointestinal tract involves the small bowel (28%), appendix (19%) and rectum (13%) ***(Pearse et al., 1990).***

The most frequently diagnosed NETs in Europe and the USA are lung, rectum and small intestine tumors, and these three have seen the greatest increase in incidence since 1974. A time-trend analysis demonstrated a statistically significant increase in incidence across all disease stages at diagnosis ***(Modlin et al., 2008).***

Surveillance Epidemiology and End Results (SEER) data indicate an incidence of 2.47 per 10,000 in white men compared with 4.48 per 10,000 in African American men ***(Kang et al., 2007).***

Ethnic differences in the risk of developing a NET are also apparent, with a higher incidence in African-American than Caucasian patients ***(Hauso et al., 2008).***

There is a slight overall higher incidence of NETs for males (5.35) compared with females (4.76) ***(Oberg et al., 2010).***

Large, population-based studies have not shown any association between smoking or alcohol use and risk of developing NETs ***(Taal and Visser, 2004).***

The majority of NETs are carcinoid tumors. Functional and nonfunctional tumors derived from the lung, pancreas, thymus, adrenal glands, and thyroid account for a smaller proportion (0.4%) of NETs ***(Kang et al., 2007).***

Risk of carcinoid in an individual with one affected first-degree relative has been estimated to be approximately four times that in the general population; with two affected first-degree relatives, this risk has been estimated at over 12 times that in the general population ***(Hemminki and Li, 2001).***

Gastric carcinoid tumors account for three of every 1,000 gastric neoplasms ***(Modline et al., 2003).***

Bronchial carcinoid tumors resemble intestinal carcinoid tumors and are not related to smoking ***(Gerard et al., 2008).***

Pancreatic endocrine tumors (p-NETs) include both pancreatic neuroendocrine tumors (p-NETs) associated with a functional syndrome (functional p-NETs) or those associated with no distinct clinical syndrome (non-functional p-NETs***) (Kulke et al., 2010).***

The two most common functional p-NETs (gastrinomas, insulinomas) are considered separately, whereas the other well-

described and possible rare functional p-NETs are considered together as a group called rare functional p-NETs (RFTs) ***(Metz and Jensen, 2008).***

The incidence of gastrinomas is 0.5–2/million population/year. They are the most common functional, malignant p-NET syndrome and comprise up to 30% of these tumors ***(Ellison and Johnson, 2009).***

Insulinomas are the most common functioning neuroendocrine tumor of the pancreas, with an estimated incidence of 1–3/ million population/year ***(Vanderveen and Grant, 2010).***

The mean age at initial diagnosis is in the late 50s in several cohorts, with the majority of cases occurring in the seventh decade ***(Ito et al., 2010).***

In the largest US epidemiological database (SEER), of all cases with available information, 49% of NET were localized, 24% showed regional metastases, and 27% were associated with distant metastases ***(Yao et al., 2008).***

In contrast, in European databases distant metastases of gastroenteropancreatic (GEP) NET at initial diagnosis are more frequent, and reported in 44 to 73% in specialized centers ***(Pape et al.,2008).***