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Anti-Tumour Treatment

Treatment of pulmonary neuroendocrine tumours: State of the art and future developments

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ABSTRACT

The current classification of pulmonary neuroendocrine tumours includes four subtypes: low-grade typical carcinoid tumour (TC), intermediate-grade atypical carcinoid tumour (AC), and two high-grade malignancies: large cell neuroendocrine carcinoma and small cell lung cancer (SCLC).

Unfortunately, with the exclusion of SCLC, no large phase II and III trials for pulmonary neuroendocrine tumours have been published. Thus, several treatment approaches are available for their treatment but none of them has been validated in appropriately designed and adequately sized clinical trials. The main problem of the published studies is that they include neuroendocrine tumours from various sites of origin with different clinical behaviour. It is important that future studies consider these tumours separately. In this regard, increased awareness and referral of these patients to tertiary centres, in which a multidisciplinary management is available, may be of value.

The aim of this review is to evaluate the state of the art and discuss future developments in the management of pulmonary neuroendocrine tumours excluding SCLC which we consider should be addressed in a different issue.

Introduction

The improvement in histological diagnostic tools, including neuroendocrine markers by immunohistochemistry (IHC), has led to an increased recognition of pulmonary neuroendocrine tumours. This may explain their rapid increase in incidence, representing roughly 30% of all neuroendocrine tumours. Their incidence has been reported to be 1.35/100,000/year, with a median age at diagnosis of 64 years. Moreover, they represent about 3% of all lung cancer accounting for about 6000 new cases diagnosed per year in the United States.[1,2]

Neuroendocrine tumours are traditionally considered to be 5-hydroxytryptamine (HT) secreting and argentaffin-positive, and have been subclassified into foregut, midgut and hindgut tumours which develop via different molecular pathways.[3,4] The foregut tumours include carcinoids of the bronchus, lung, thymus, stomach, the first portion of the duodenum, and pancreas.

The aim of this review is to evaluate the state of the art and future developments in the management of pulmonary neuroendocrine tumours excluding small cell lung cancer (SCLC) which we consider should be addressed in a different issue.

Classification

The World Health Organization (WHO) classifies the pulmonary neuroendocrine tumours in four subtypes: low-grade typical carcinoid tumour (TC), intermediate-grade atypical carcinoid tumour

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Table 1
Clinic–biologic characteristics of pulmonary neuroendocrine tumours.

Characteristics	Typical carcinoid	Atypical carcinoid	Large cell neuroendocrine carcinoma
% of lung tumours	1–2	0.1–0.2	2–3
Grade of differentiation	Low	Intermediate	High
Pathologic features	<2 mitoses/2 mm^2	2–10 mitoses/2 mm^2	>10 mitoses/2 mm^2
Lymph node metastases at presentation	5–15%	40–50%	60–80%
Distant metastases	3%	20%	40%

(AC), and two high-grade malignancies, large cell neuroendocrine carcinoma (LCNEC) and SCLC.[5] TC and AC are categorized together as carcinoids, LCNEC is considered a subgroup of large-cell carcinomas. In WHO diagnostic criteria TCs, which account for 1–2% of lung tumours, are classified by pathologic features with <2 mitoses/2 mm^2 of viable tumour, no necrosis, and 0.5 cm or larger in size. ACs account for 0.1–0.2% of lung tumours and have 2–10 mitoses/2 mm^2, necrosis, or architectural disruption. LCNECs account for about 2–3% of all lung cancers and are characterized by >10 mitoses/2 mm^2 and cytological features of a large-cell carcinoma (Table 1).[5] The carcinoid group is distinct from the more undifferentiated and aggressive LCNEC and SCLC[5] which are strongly related to tobacco smoking habit[6], whereas a correlation with carcinoids and tobacco smoking is uncertain. Several peptide and amine markers such as chromogranin A (CgA), neurone-specific enolase (NSE), serotonin, synaptophysin, and adrenocorticotrophic hormone (ACTH) have some utility in establishing the differential diagnosis.[5] Somatostatin receptors (SSTRs) are a family of five widely distributed G-protein-coupled receptors that mediate different intracellular signalling pathways involved in cell proliferation, differentiation and angiogenesis.[7,8] Indeed, in clinical practice the presence of SSTRs should be demonstrated to justify patient's selection for somatostatin analogue therapy. A study compared the SSTR types 2A and 3 tissue distribution by IHC with pathological and clinical data of a series of 218 pulmonary neuroendocrine tumours (24 metastatic TCs, 73 ACs, 60 LCNECs and 61 surgically resected SCLC). A high heterogeneity was reported for SSTRs distribution with a significant progressive decrease from low- to high-grade forms. The SSTR type 2A was strikingly overexpressed in metastatic TCs as compared with ACs and clinically benign TCs.[9] Moreover, SSTR2a and SSTR5 messenger-ribonucleic acids (mRNAs) have been demonstrated to be detectable in peripheral blood of pulmonary neuroendocrine tumours affected patients using real-time quantitative PCR, with a good conformity with octreoscan, showing a high sensitivity and suggesting that this method could represent a useful tool in the clinical management of these tumours.[10]

Genetic data have been proposed for a better classification of pulmonary neuroendocrine tumours. Abnormal expression or loss of heterozygosity (LOH) and point mutations of the p53 locus on chromosome 17p13 have been detected in about 4% of TC, 29% of AC, and 80% of LCNEC supporting the hypothesis that TC, AC and LCNEC are genetically distinct from each other.[11–14] Moreover, the frequency of p53 protein expression was found to be 0% for TC, 20% for AC, and 86% in LCNEC, suggesting that it could be used to distinguish between subtypes.[15] Telomerase activity is present in <10% of TC but in about 90% of LCNECs[16] as also E-cadherin and beta-catenins, transmembrane glycoproteins involved in epithelial cell–cell adhesion, which are expressed in about 85% of LCNECs and 37–50% of carcinoids.[17] Unfortunately, their utility in classifying these tumours subgroups remains uncertain due to the different incidence and classifications of the diverse genetic alterations reported.

Two more rare conditions related to pulmonary neuroendocrine tumours are the tumourlets and the diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH). Tumourlets are incidental histological findings of nodular aggregates of neuroendocrine cells in association with airways that demonstrate morphology similar to those of carcinoid tumours which extend beyond the basement membrane and measure <0.5 cm in greatest diameter. DIPNECH is thought to represent a pre-invasive lesion of carcinoid tumours. Histologically, it is defined as pulmonary neuroendocrine cells (PNEC) hyperplasia confined to the respiratory epithelium without penetration through the basement membrane. DIPNECH represents the earliest manifestation of a neuroendocrine disease in the bronchopulmonary system and a preneoplastic lesion for pulmonary neuroendocrine tumours.[18]

Pulmonary carcinoids may occur in about 5% of cases as a component of the familial endocrine cancer syndrome multiple neuroendocrine neoplasia 1 (MEN1), although the majority occur as sporadic isolated tumours. MEN1 is an autosomal dominant disorder associated with the gene locus on 11q13 and includes neoplasms of the pituitary, pancreas, and parathyroid. In patients with MEN1, screening for pulmonary carcinoids with computed tomography (CT) imaging of the chest is recommended.[19]

Staging

Despite the old TNM staging system did not apply to carcinoids, most publications on TCs and ACs use the TNM staging system employed for non-small cell lung cancer (NSCLC) and are able to demonstrate prognostic significance for the different stages. In fact, among these, a large analysis of about 800 pulmonary carcinoids showed that 87% of TC present without lymph node metastases, 10% and 3% exhibited N1 and N2 disease involvement, respectively. On the contrary, 43% of AC were lymph node-negative, 29% were N1, 14% were N2 and 14% were N3, respectively. These data underline that TC and AC metastasized usually to intrathoracic lymph nodes, but in 3% for TC and 21% for AC distant metastases occur (Table 1).[20]

A total of 513 carcinoids collected for the International Association for the Study of Lung Cancer (IASLC) Staging Project database and 1619 cases from the Surveillance Epidemiology and End Results (SEER) database were analysed. T status was a statistically significant predictor of survival for both the SEER ($p < 0.0001$) and the IASLC databases ($p = 0.0156$). N status showed significant survival correlations in both data sets ($p < 0.0001$). The effect of M status was significant ($p < 0.0001$) within the SEER data and not studied in the IASLC cases, which were almost exclusively M0. So, the 7th TNM classification is generally useful for staging also pulmonary neuroendocrine tumours.[21]

No specific mentions have been made concerning the staging of LCNEC in all previous TNM staging systems.

Diagnosis

The majority of patients are symptomatic at presentation with cough, haemoptysis, and post-obstructive pneumonia. Carcinoid syndromes at presentation, including symptoms related to serotonin secretion such as diarrhoea, flushing, wheezing, and carcinoid heart disease, are rare (1–3%), and usually observed in case of liver