Lung Cancer xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Review

Systemic therapy for pulmonary carcinoids

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ARTICLE INFO

Article history:
Received 24 July 2015
Received in revised form 25 August 2015
Accepted 27 August 2015

Keywords:
Anti-angiogenesis
Chemotherapy
Lung cancer
Pulmonary carcinoid
Peptide receptor radiotherapy
Targeted therapy

ABSTRACT

Between 25 and 33% of neuroendocrine tumours arise in the lung as low-grade typical pulmonary carcinoids (TPC), intermediate-grade atypical pulmonary carcinoids (APC), and high-grade large cell neuroendocrine or small cell carcinomas. The relatively uncommon incidence and prevalence of PCs are progressively increasing. However, data regarding systemic treatment for PCs are limited, controversial and based on old reports with few randomized or placebo-controlled trials, small sample sizes, or including tumours with very different behaviours. Moreover, conclusions are generally extrapolated from the outcome of extra-pulmonary carcinoids, treatment arms are not well defined or mix different therapies, and the indolent nature of some PCs is not adequately considered in designing control arms. Here, we reviewed and discuss current recommendations regarding systemic treatments for PCs.

1. Introduction

Neuroendocrine tumours and carcinomas (NET/C) include a wide variety of malignancies with different origin, molecular expression, and clinical behaviour. Between 25 and 33% of them arise in the lung and range from low-grade typical pulmonary carcinoids (TPC), to intermediate-grade atypical pulmonary carcinoids (APC), and to high-grade large cell neuroendocrine (LCNEC) or small cell carcinomas (SCLC) [1,2] (Table 1).

The incidence and prevalence of PCs are progressively increasing perhaps due to a higher awareness and accuracy of diagnosis and due to the indolent nature of the disease, respectively. With an incidence of 0.2–2 $\times 10^5$ cases/year, PCs represent 1–2% of lung malignancies [2–7] and are slightly commoner in women and Caucasians [3,8]. TPCs are 8–10 fold more frequent than APCs and trend to present in younger patients between the 4–6th decades of life [8–11]. Furthermore, PCs are the commonest primary lung neoplasm in childhood and adolescence [12].

PCs origin is in the Kulchitsky cells, which able them to secrete bioactive peptides. Smoking may impact as a risk factor for their development, especially for APCs [10,13,14], and *MEN1*-gene alterations may be harboured by sporadic PCs. However, PCs rarely present as multiple endocrine neoplasia [3,11].

As Tables 1 and 2 summarize, tumour grade influences clinical behaviour with a significantly higher incidence of distant and lymph node metastases in APC than in TPC, as well as rate of local and distant relapse [15–21]. APCs consistently demonstrate lower disease-free (DFS) and overall survival (OS) [16,21–23].

The 7th edition of the UICC TNM system is recommended for PC staging since different series have independently confirmed a significant impact on survival from T ($p = 0.01$), N ($p < 0.0001$) and M descriptors ($p < 0.0001$). In the same way, pathology should report the involvement status and distance of resection margins as well as the relatively common presence of incidental neuroendocrine hyperplasia [2,20,21]. By contrast, the presence of diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH), a pre-invasive lesion increasing risk of PC and defined as the proliferation of <0.5 cm neuroendocrine 'tumorlets' within the bronchial epithelium and extending beyond the basement membrane with a low Ki-67 index, no mitosis or necrosis, is rare [2,24–26].

PCs can occur throughout the lung parenchyma, being right-sided in 59–62% of cases. The higher incidence of TPCs, with mean tumour size of 25–34 mm, is associated with central location in 70–75% of PCs [15,27,28]. APCs trend to be larger, more commonly peripheral tumours, with occasional nodal skip metastases [16,23]. Between 30 and 50% of PCs presents as asymptomatic incidental findings. However, central location and high vascularization could result in symptoms including haemoptysis, cough, wheezing, recurrent obstructive pneumonia, atelectasis, pain, or dyspnoea for many years before diagnosis.

In contrast to gastrointestinal NETs, neurosecretory syndromes such as Cushing's (0.6–6%) or carcinoid (1.5–5%), acromegaly (2.4%), encephalitis (1.6%), myasthenia gravis (0.6%), inappropriate antidiuretic hormone secretion, hypercalcemia, or hypoglycaemia are

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http://dx.doi.org/10.1016/j.lungcan.2015.08.018
0169-5002/

Table 1
Features of pulmonary tumours with neuroendocrine morphology.

WHO 2000	WDET	WDEC	PDEC	
WHO 2010	NET G1	NET G2	NEC	
	TPC	APC	LCNEC	SCLC
Percentage	2%	0.2%	3–5%	14–17%
Morphology	Uniform polygonal cells in organoid or trabecular patterns.	Large neuroendocrine cells	Smaller than 3 resting lymphocytes cells	
Size	Size is not a useful discriminator.			
Grade	Low	Intermediate		
High				
N/C	Not useful to distinguish. Moderate amount of cytoplasm with an eosinophilic hue.		Low (abundant pink cytoplasm)	High (scant cytoplasm)
Nuclear chromatin	Not useful to distinguish. Finely granular nuclear chromatin. Frequent "salt and pepper" appearance		Vesicular, coarse or fine	Finely granular
Nucleoli	Not useful to distinguish		Frequent (not always present)	Absent or inconspicuous
Nuclear molding	Not useful to distinguish		Rare	Present
Nuclear smearing	Not useful to distinguish		Rare	Frequent
Cell borders	Not useful to distinguish		Distinct	Indistinct
Mitotic rate[a]	0–1	2–10	≥11	
Median mitotic rate	0–1/2 mm^2	2–10/2 mm^2	70/2 mm^2	80/2 mm^2
Ki67	<5%	5-20%	50-100%	80-100%
Necrosis	No	Often punctate	Present in large areas	
IHC	Chromogranin, synaptophysin, CD56 (Not required)	Chromogranin, synaptophysin, CD56 (Not required)	Positive staging for ≥1 marker	Chromogranin, synaptophysin, CD56 (Not required)
Mixed forms associated with NSCLC	Not reported		Reported	
Precursor	DIPNECH		No	
Average age	40s	50s	<60s	>60s
Association with smoking	−/+	−/++	++	+++
Location	Mainly central	Often peripheral	Often peripheral	Central
5yOS	90–95%	60–70%	10–40%	5–15%

5yOS five-year overall survival; DIPNECH diffuse idiopathic neuroendocrine cell hyperplasia; IHC immunohistochemistry; HPF high power field; HPNL Hyperplastic and preneoplastic lesions; LCNEC large cell neuroendocrine cancer; MANEC mixed adenoneuroendocrine carcinoma; MEEC mixed exo/endocrine carcinoma; N/C nuclear/cytoplasmic ratio; NEC neuroendocrine large or small cell carcinoma; NET neuroendocrine tumor; PDEC poorly-differentiated endocrine/small cell carcinoma; SCLC neuroendocrine small-cell lung cancer; TLL tumor-like lesions; WDEC well-differentiated endocrine carcinoma; WDET well-differentiated endocrine tumour.

[a] Mitotic rate per 10HPF.

Please cite this article in press as: D. Marquez-Medina, S. Popat, Systemic therapy for pulmonary carcinoids, Lung Cancer (2015), http://dx.doi.org/10.1016/j.lungcan.2015.08.018