Long−term follow up of patients affected by pulmonary carcinoid at the Istituto Nazionale Tumori of Milan: a retrospective analysis

Pusceddu S[1], Catena L[1], Valente M[1], Buzzoni R[1], Formisano B[1], Del Vecchio M[1], Ducceschi M[1], Tavecchio L[2], Fabbri A[3], Bajetta E[1].

[1]Medical Oncology Unit 2, Fondazione IRCCS "Istituto Nazionale dei Tumori", Milan 20133, Italy.
[2]Thoracic Surgery Unit, Fondazione IRCCS "Istituto Nazionale dei Tumori", Milan 20133, Italy.
[3]Pathology Unit, Fondazione IRCCS "Istituto Nazionale dei Tumori", Milan 20133, Italy.

ABSTRACT   Neuroendocrine tumors of the lung involve an heterogeneous group of tumors representing a wide range of histological variants, from well-differentiated typical carcinoid (TC) tumors to poorly differentiated small cell carcinomas. The epidemiology, clinical outcome, and management of these neoplasms differ significantly from other lung malignancies. The main aim of this report consists in describing the single Center experience of the Istituto Nazionale Tumori of Milan on neuroendocrine lung tumors, with an emphasis on bronchopulmonary carcinoid subtypes. From 1986 to 2009, 91 cases of carcinoid tumors were diagnosed; these were divided in two series, according to typical (66 patients) or atypical (25 patients) histotypes. These two groups were compared in relation to various features, including pathologic classification, clinical behavior, treatment modalities and long-term survival. At the moment of diagnosis 11 patients had locally advanced/metastatic disease, while 80 patients showed non metastatic disease. The comparative analysis between typical and atypical series disclosed significant differences in terms of long-term survival; in fact, 5-year and 10-year survival rates were 98 % and 94 % for the first carcinoid series versus 76 % and 18 % for the atypical series, respectively (p<0.001). The median overall survival (OS) was 76 months (range 3-182) for atypical carcinoids and has not yet been reached for TCs patients.

KeyWords: carcinoid; lung cancer; neuroendocrine; pulmonary

Introduction

Neuroendocrine (NE) lung tumors originate from a population of NE cells normally present in the bronchoalveolar structures and characterized by secretory activity and ability to uptake and decarboxylate the amine precursors (APUD System cells) (1). These NE phenotypical and morphological characteristics are present within a broad spectrum of histologies of lung NE tumors, from relatively indolent typical carcinoids (TC) to histologically high-grade, biologically aggressive tumors.

The spectrum of pulmonary NE tumors, according to the current WHO classification by Travis, includes four subtypes characterized by increasing aggressiveness: typical carcinoid (TC), atypical carcinoid (AC), large-cell neuroendocrine carcinoma and small cell carcinoma. Among these, TC and AC tumors are considered

low-grade and intermediate-grade NE neoplasms, respectively (2). Bronchopulmonary (BP) typical and atypical carcinoid tumors are uncommon, representing 2% of all pulmonary neoplasms; these variants are associated with relatively slow growth, and generally show a favorable outcome (3). The annual incidence is approximately 2.3 to 2.8 cases/1 million population (4,5). Most of these cases consisted in typical carcinoids (80-90%), and occurred more frequently in the fifth and sixth decades; it's interesting to underline that they represented the most common lung tumors in childhood. The female/male ratio is 1.6:1 (5).

Even if both typical and atypical carcinoids are the expression of NE lung tumors bearing the best prognosis and outcome, these two histotypes show some well known differences in terms of histologic features, molecular biology, pattern of spread and treatment modalities.

The most important differential criterion between TCs and ACs is represented by the mitotic count.

The TCs have < 2 mitoses per mm^2 in 10 high-power fields (HPF) without signs of necrosis, while ACs are characterized by 2 to 10 mitoses per mm^2/10 HPF and/or foci of necrosis.

In combination with the histologic appearance, the cell proliferation characterized by low labeling index Ki67 (MIB1) <20% seems to be the most useful marker to distinguish the low-grade and the high-grade of malignancy subgroups within the bron-

chopulmonary NETs. In particular, the immunoreactivity for nuclear markers (especially Ki67) is easily accessible and may be helpful in the differential diagnosis between TC/ACs and small-cell carcinomas, being high grade NE tumors characterized by a proliferative cell fraction extremely higher than that of carcinoids (MIB1 >50%) (6). Several peptide and amine markers, including Chromogranin (CgA), neuron-specific enolase (NSE), serotonin, synaptophysin, and adrenocorticotropic hormone (ACTH), can provide us with further tools in order to better establish a differential diagnosis (6).

Molecular genetic changes may be useful as an adjunctive element to differentiate typical and atypical carcinoids. Retinoblastoma gene (13q13) and p53 (17p13) mutations, multiple endocrine neoplasia (MEN) 1 gene activation (11q13), and telomerase activity, are particularly frequent in atypical carcinoids if compared with the typical ones (7).

Although both tumors are malignant, they have a usually benign behavior, thus being rarely responsible for the death of patients, even after an extensive period of follow-up. However, ACs are more aggressive than TCs, metastasizing more commonly both to regional lymph nodes and distant sites.

Generally, pulmonary TCs appear as central lesions, whereas ACs are more commonly located peripherally. Bronchopulmonary carcinoid tumors have a propensity to develop in the right lung and most of them (90%) are confined to the bronchus (8), while the remaining 10% are located in the lung parenchyma, rarely in the main carina or trachea.

Carcinoids, as other neuroendocrine tumors, may secrete hormone-like substances such as adrenocorticotropic hormone (ACTH) and arginine vasopressin, thus causing paraneoplastic syndromes. The classic carcinoid syndrome is very rare in patients with pulmonary carcinoids (+/- 2%) (9). Presenting symptoms in both the subtypes can be cough, hemoptysis, or signs of bronchial obstruction; in some cases, the patients can be asymptomatic.

The treatment of choice is surgery for localized disease. In advanced or metastatic disease no effective medical treatment exists (10,11). The aim of this retrospective analysis is to review low-grade lung NETs treated at our institution in order to assess any correlation between the histological subtypes and clinical behavior, treatment response and long-term survival.

Patients and methods

We retrospectively reviewed a cohort of 91 consecutive patients affected by bronchopulmonary carcinoids referred at the Medical Oncology Unit 2, National Cancer Institute of Milan, during a 23-year period from 1986 to 2009.

The analyzed data included patients' age and sex, presenting symptoms, stage at diagnosis, histophatological findings, presence or absence of carcinoid syndrome, In-111-labeled OctreoScan (scintigraphy with radiolabelled octreotide), treatment modalities and overall survival (OS). The histological subtypes were classified according to the 1999-2004 Travis-WHO classification criteria by pathologists from our Institution (2).

For staging and follow-up we used brain, chest and abdominal computed tomography scan (whole body CTscan). In case of suspected relapse, we have also performed Octreoscan to integrate CT over the last 15 years in order to better define the staging at diagnosis and the consequent treatment plan. Fibrobronchoscopy was performed in those patients who had endobronchial carcinoids or in case of suspicion of bronchial recurrence. The Kaplan-Meier product limit estimator was used to graphically display the survival curves, with death from any cause as outcome; Mantel-Cox log-rank test was used to compare survival between different groups. A p value of <0.05 was considered statistically significant.

Results

The patients' baseline characteristics are summarized in Table 1. The cohort consisted of 33 men and 58 women, with a median age of 56 years (range 17-82), affected by typical carcinoids (66 cases) and atypical carcinoids (25 cases). Some patients showed accompanying pathologies including hypertension (25 patients), diabetes mellitus (10 patients) and cardiovascular diseases (4 patients). The

Table 1 Patient's characteristics

	Typical Carcinoid	Atypical Carcinoid
Age, years		
Median	55.5	59
Range	(17-82)	(27-78)
Gender		
Female	47	11
Male	19	14
total	66 (72.5%)	25 (27.5%)
Paraneoplastic syndrome		
No	4 (6%)	-
Stage at diagnosis		
Early stage	60	20
Locally advanced or metastatic	6	5

majority of patients are asymptomatic, and, in the remaining patients, the most notable presenting signs/symptoms were invariably respiratory consisting in hemoptysis, cough, ronchi, and dyspnea other than weight loss. According to the natural history of these malignancies, only 4 patients had carcinoid syndrome with facial flushing and diarrhea as the commonest symptoms. Octreoscan and positron emission tomography (PET) scan were performed at diagnosis in 49 patients as staging procedures, providing us with an important help for the detection of primary tumor or disease recurrence.

Treatment

Of the 91 patients reviewed at our Institute, 80 (88%) were classified in early stage at diagnosis, 60 of whom (75%) were classified as CTs and 20 (25%) as ACs, respectively.

All patients underwent radical surgery and no adjuvant treatment was performed after surgery.

After surgical treatment, 24 patients (30%) developed a recurrent tumor (11/60 CTs and 13/20 ACs), being liver the most frequent site of distant relapse in 67% of all the histotypes. Other sites of relapse included lung (37%), lymph nodes (33%) and bone (17%) with a similar distribution between TCs and ACs. Locally advanced disease and distant metastases were observed in 11(12%) patients (6 TCs and 5 ACs); the majority of these patients had two or more sites of distant metastases, being liver and lung the most frequent targets.

Nevertheless, in this prolonged period of observation of such retrospective study, all patients with relapsed, advanced or metastatic disease were suitable for medical treatment. In these series of patients, 23 were treated with somatostatin analogs, 10 with 5-FU or CDDP-based chemotherapy.

Survival analysis

The median overall survival (OS) calculated for ACs was 76 months (range 3-182) while, up to date, for TC patients the median

	Total	Dead	Surv*
A	25	10	76
B	66	4	n.r.

A) Atypical carcinoid(25) ——
B) Typical carcinoid(66) ——

No.at risk 0 24 48 72 96 120
25 17 13 7
66 66 33 24

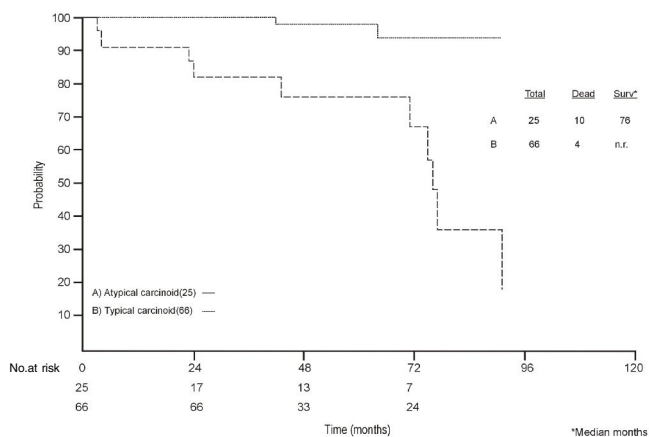Time (months) *Median months

Fig.1   Overall survival by histology: TCs versus ACs.

OS has not yet been reached (Fig 1).

Five and ten-year survival rate were 98 and 94% for TCs and 76 and 18% for AC, respectively (p < 0.001).

Discussion

Pulmonary carcinoids are rare (accounting for less than 2% of all bronchial tumors) (3), and they represent a spectrum of neuro-endocrine tumors with different behaviors and prognoses depending on histopathological features and differentiation. We reviewed retrospectively the histology of our bronchopulmonary carcinoid tumor series using the 1999 Travis classification with the aim to gather information about clinical outcomes and survival related to histopathological subtype and stage.

Our data on the demographic characteristics demonstrated a different gender distribution in both typical and atypical histotypes. The female/male ratio is 2.5:1 and 1:1.5 in TC and AC, respectively; then, according to literature, the patients with atypical carcinoids were generally older at presentation than those bearing typical subtype (median 59 vs 55 years, respectively). These findings, although with limited numbers of patients, confirm the relationship histological switching from low- to high grade, tumor aggressiveness, increasing age and male incidence for these tumor types, as postulated by other authors (4,12); in fact, we confirm the hypothesis that male sex and older age can be a negative prognostic factors in BP carcinoid tumors.

Typical carcinoids excellent long-term overall survival rate, while atypical carcinoids showed worse survival rate, thus the aggressiveness of this form and its disappointed prognosis especially in advanced stages. The 5-year survival rate for neuroendocrine tumors of the lung rang from 87 to 97% for TCs and from 56 to 77% for ACs (12-14). The very favorable prognosis for TC is justified by the low percentage of distant metastases after radical surgery (5-20%); on the contrary, 30-70% of individuals with ACs exhibit regional lymph node or distant metastatic disease (15). In fact, Fink et al. reported that TC patients had N1 disease in10% of cases and N2 in 3% (no N3 observed), while AC patients had N1 in 29% of cases, N2 in 14% and N3 in 14%. Distant metastases have usually been observed at the liver, skeleton, central nervous system, skin and mammary glands (3% for TC and 21% for AC) (5).

AC tumors have demonstrated in most of the studies a poorer prognosis if compared to TC, due to a major biological aggressiveness; we have confirmed these characteristics also in our experience, where the comparative analysis between the two subtypes disclosed statistically significant difference in overall survival (Figure I). TCs showed a significant better survival than ACs (5-year-survival rate 98% and 76%, respectively), according to the range of the rates reported previously, with a lower percentage of recurrence of TC (18%), in comparison to AC (65%), after surgery in the early stage.

The results of this retrospective analysis also confirm that Travis classification is fundamental in the clinical management of

carcinoid tumors in order to determine the prognosis of both typical and atypical subtypes. Consequently, these data support the fact that accuracy of the pathological diagnosis and clinical staging are essential to decide the appropriate management of such disease. When the tumor is accessible (35-70% of BP carcinoids), fibro-broncoscopy remains the most important tool for diagnosing BP carcinoids, while the fine-needle aspiration through computed tomography scan (CTscan), is preferred for peripheral lesions (7). Mediastinoscopy, video-assisted thoracic surgery, and thoracotomy are other alternatives in case of not feasibility of less invasive diagnostic procedures.

CT scan is recommended to define the clinical stage (TNM) at diagnosis and during the follow up, and newer modalities of scintigraphy using radiolabelled somatostatin analogs, such as Octreoscan or (68) Ga-DOTATOC PET, are useful in case of doubts regarding the nodal status, the tumor diffusion and the identification of an unknown primary tumor site. Regarding the biochemical markers, measurement of urine 5-hydroxyindole-3acetic (5-HIAA) has an 88% specificity for the detection of 5-HT producing bronchopulmonary NE tumors. CgA is a sensitive marker of NETs, even if it can be normal in carcinoids until metastatic disease develops (16).

When feasible, radical surgery offers the only chance of cure, representing the treatment of choice for localized disease (10). The medical treatment of metastatic disease includes biotherapy with somatostatin analogs, possibly associated with interferon α -2a, and chemotherapy. Somatostatin analogs can provide good symptomatic relief, prolonging the time to progression in low-grade histotypes; however, most of the published data refer to small numbers of patients, thus no statistically significant conclusions can be taken out (11). The use of various chemotherapeutic agents (doxorubicin, 5-fluorouracil, dacarbazine, cisplatin, etoposide, streptozotocin and carboplatin), can produce not durable objective responses or stabilizations of disease (7). More promising results, especially ACs, have been reported using targeted radiotherapy with 111In octreotide and 131I meta-iodo-benzyl-guanidine (MIBG) (13). Liver embolization with gel foam has been used in few patients with symptomatic disease and predominant tumor burden localized at liver. Transient stabilizations and objective responses have been occasionally observed (17). Generally, in patients affected by TCs or ACs bearing an indolent course, octreoscan positivity and/or carcinoid syndrome, our first-line treatment consists in somatostatin analogs (LAR octreotide/lanreotide). Following the failure of this therapeutic regimen, we have switched to 5 fluorouracil (5FU)-based chemotherapy, or polychemotherapy including the combination of 5-fluorouracil, dacarbazine , and epirubicin (FDE regimen, 5FU + Dacarbazine + Epirubicine), or capecitabine plus oxaliplatin (the XELOX regimen), treatment schemes that had demonstrated activity in BP carcinoids in our previous clinical trials (18-23). Patients having shown progressive disease during therapy based on these regimens were treated with either cisplatin plus etoposide or metabolic radiotherapy. Liver chemo-embolization was used as second or third line treatment when most of the tumor burden was located at liver.

Conclusion

Many questions remain to be answered regarding the knowledge of biological mechanisms of BP neuroendocrine system and concerning the optimal treatment of typical and atypical carcinoid tumors. In particular, what should be the best surgical strategy for correct staging in carcinoid tumors (adequate lung resection with or without complete mediastinal nodal dissection) and the role of adjuvant chemotherapy or mediastinal radiotherapy in AC tumors with lymph node involvement are still under debate. Regarding the medical treatment of metastatic disease, further studies are necessary to clarify histology-specific mortality and tumor treatment sensitivity, also considering genetic characteristics and other biological aspects. Traditionally, cytotoxic agents are of limited efficacy in the treatment of neuroendocrine tumors. Recent investigations have contributed to identify a number of biological features in this family of neoplasms that could represent targets for tailored treatment. NETs seem to have an extraordinary tumor vascularization, as documented by high expression of proangiogenic molecules such as vascular endothelial growth factor, overexpression of certain tyrosine kinase receptors such as EGFR, IGFR and by activation of the downstream signaling pathway (PI3K-AKT-mTOR). Various clinical trials for patients with carcinoids are currently recruiting patients. The main objective consists in setting up a precise targeted therapeutic strategy according to the biologic and genetic advances.

Acknowledgements

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