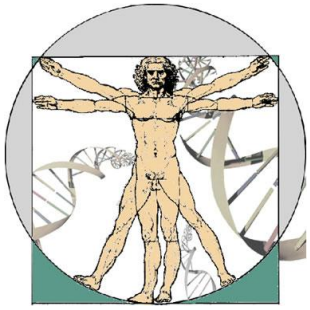


Laboratory of Experimental Physiology
"Fysiologeion"
Post-Graduate Program: "Molecular and Applied Physiology"
Medical School
National and Kapodistrian University of Athens

LARGE CELL NEUROENDOCRINE TUMORS OF THE LUNG (LCNET).

A SINGLE ONCOLOGY DEPARTMENT EXPERIENCE.

Master's Degree Thesis

Apostolos M. Laskarakis

ATHENS 2013

The Thesis is dedicated to my beloved wife and sister

Acknowledgments

I would like to express my deepest gratitude to all those who helped and supported me throughout the duration of this research. In particular, I am heartly thankful to my supervisor, Professor Michael Koutsilieris, for his patience and guidance, that helped me not only in the completion of this thesis but also throughout the duration of this two year scientific journey in the world of Molecular and Applied Physiology. He was always there to meet and help me think through my problems.

I am also deeply indebted to my Director in the Oncology Department of «Evaggelismos», Athens General Hospital, Dr. Michael M. Vaslamatzis, who gave me the opportunity to conduct my study and also commented and reviewed my work on a very short notice. He is a true mentor for me.

I would like also to thank the rest of my thesis committee: Professor George Vaiopoulos and Professor Gabriel Karatzas who not only dedicated their precious time to evaluate my thesis but also took along with Professor Koutsilieris the initiative to establish this Post – Graduate Programme, giving me the opportunity to fulfill high level postgraduate studies in my homeland.

I am also greatly thankful to my friend and colleague George Papaxoenis for his help with statistical analysis.

Last but not least, I thank my parents, my wife, my child and my sister for believing in me and for their continuous encouragement and love. Without them this would not have been possible.

Introduction

Large- cell neuroendocrine carcinoma (LCNEC) is a relatively rare pulmonary neuroendocrine tumor with aggressive biological behaviour. Its diagnosis is challenging, while the best therapeutic approach is still dubious.

Goal of my Thesis is to present up to date information from international bibliography as well as to depict the results of my study in patients with large – cell neuroendocrine tumors of the lung.

It consists of two main parts: i) a review article, where the most recent knowledge about the pathological characteristics, diagnosis, prognostic markers and treatment modalities for this neoplasm is depicted, and ii) a study of patients with large- cell neuroendocrine tumors of the lung, conducted in the Oncology Department of «Evaggelismos», Athens General Hospital.

In this study, epidemiological, clinical and immunohistological characteristics as well as treatment results of nineteen (19) patients with LCNEC treated in the Oncology Department of «Evaggelismos» Hospital from April 1997 to January 2013 were reviewed. According to the results of our study, the stage of the disease along with the performance status of the patients played a vital role in the overall outcome and survival.

Moreover, disease burden seemed to play a prognostic role.

Review article

Large cell neuroendocrine carcinoma of the lung.

Apostolos M. Laskarakis

Introduction

Large - cell neuroendocrine carcinoma is a relatively rare lung tumor as it constitutes up to 3% of all lung cancers [1, 2]. It is a part of a spectrum of tumours called pulmonary neuroendocrine tumours which were first writtenly described by R. Laennec in a posthumously published report in 1831, where he was referring to an intrabronchial mass probably a bronchopulmonary carcinoid [3]. Pulmonary neuroendocrine tumors were classified into three major categories: Typical carcinoids, atypical carcinoids and small cell lung cancer until 1991, when Travis et al. described a distinct subset of tumors with prognostic spectrum similar to small cell lung cancer called large-cell neuroendocrine carcinoma [4, 5].

According to most recent knowledge, the spectrum of pulmonary neuroendocrine tumors includes tumors with neuroendocrine morphology such as the low- grade typical carcinoid (TC), the intermediate- grade atypical carcinoid (AC) and the high-grade large-cell neuroendocrine carcinoma (LCNEC) and small cell lung cancer (SCLC) [6]. They account for about 20-25% of all invasive lung cancers. Small cell lung

cancer is the most frequent neuroendocrine malignancy representing 15-20% of invasive lung cancers while LCNEC accounts for 3% of all lung cancers [7, 8]. Large-cell neuroendocrine can be difficult to diagnose while the optimal treatment is not yet established [8].

Pathological characteristics

According to 1999 and 2004 World Health Organization (WHO) classifications, LCNEC is a high – grade, non small cell neuroendocrine carcinoma and a distinct subtype of pulmonary large-cell carcinoma, a form of non-small cell lung cancer (NSCLC) [9, 10]. According to Travis et al., there are four different categories of neuroendocrine phenotypes in large-cell carcinomas: i) LCNEC with neuroendocrine features identified by light microscopy as well as immunohistochemistry and electron microscopy, ii) Large-cell carcinoma with neuroendocrine morphology (LCNEM) but without neuroendocrine differentiation identified by electron microscopy, iii) Large-cell carcinomas with neuroendocrine differentiation (LCC-NET) but without neuroendocrine morphology documented by immunohistochemistry or electron microscopy and finally iv) classic large-cell carcinoma (LCC) without both neuroendocrine morphology and differentiation [5, 10].

Large-cell neuroendocrine tumours are characterized by their neuroendocrine morphology with organoid nesting, trabecular pattern,

palisading and rosette-like structures and their high mitotic rate of 11 or more mitoses per 10 high power fields (average 60- 80 mitoses) which is the main criterion separating LCNEC and SCLC from atypical carcinoids [8, 11].

Other pathological characteristics include: non-small cell cytologic features such as large- cell size, low nuclear/cytoplasmic ratio, prominent nucleoli and often large zones of necrosis and neuroendocrine differentiation manifested by immunohistochemistry with antibodies such as chromogranin, synaptophysin and CD56 or by electron microscopy, while they do not express high molecular weight cytokeratines which are typical for SCLC [9, 12, 13]. Lastly, in 41-75% of cases thyroid transcription factor-1 (TTF-1) may be positive [14,15].

Molecular markers

Compared to low-grade neuroendocrine tumors or to classic large–cell carcinomas, LCNEC have a much higher proliferation index with staining of 50 – 100% of tumor cells [16]. Moreover abnormal expression, loss of heterozygosity and point mutations of the p53 locus have been detected in about 80% LCNEC [17,18].

Telomerases are enzymes which play vital role in the synthesis of DNA. There is evidence that high telomerase activity is present in LCNEC and in SCLC compared to low-grade carcinoma tumors, while

high expression of Bcl-2 antiapoptotic gene and p21 marker of angiogenesis is detected in LCNEC [19, 20]. In addition to the above, in 2005 Rossi et al., reviewed the immunohistochemical expression and mutational status of the receptor tyrosin kinase (KIT) and platelet derived growth factor alpha and beta (PDGFRalpha , PDGFRbeta) and MET in 83 patients with LCNEC. According to their study, LCNEC strongly expressed KIT, PDGFRalpha, PDGFRbeta and MET in 63%, 60,2%, 82% and 47% of patients respectively but no mutations in the exons encoding for the relevant juxtamembrane domains were detected, while MET expression was significantly connected with survival, providing a potential marker for future targeted therapies [21].

E-cadherin and beta–catenins involved in epithelial cell-cell adhesion are strongly expressed in LCNEC and SCLC than in low-grade carcinoids, while the down regulation of E-cadherin – beta catenin complex seems to be involved in LCNEC tumor progression [22, 23].

It is well known that epidermal growth factor receptor (EGFR) - Tyrosin Kinase inhibitor (TKI) has been effective for NSCLC patients with specific EGFR mutations in exons 19 or 21 [24]. Therefore, in 2011, Iwoda et al. analyzed 13 LCNEC for the presence of EGFR gene mutation. Only a single EGFR mutation (a silent mutation in codon 725) was detected supposing that EGFR-TKI is not likely to be an effective therapy for patients with LCNEC [25]. In contrary to the above, a high

expression of vascular enthothelial growth factor (VEGF) has been detected suggesting a possible role of anti-VEGF therapy in the future for these patients [25]. Most recently, two cases of large- cell neuroendocrine carcinoma with an EGFR mutation have been reported. In the first case the LCNEC progressed despite treatment with EGFR-TKI suggesting that was a case of LCNEC carrying an EGFR mutation which may have developed from adenocarcinoma, while at the other occasion the LCNEC with an EGFR mutation responded to treatment with EGFR-TKI gefitinib [26, 27]. Lastly, in 2013, Odate et al. found that tropomyosin-related kinase B (TrKB) and its ligand brain-derived neurotrophic factor (BDNF) enhance tumor progression and invasion in LCNEC suggesting a potential target for future therapies [28].

Epidemiology – clinical presentation

Most of the patients with LCNEC are male with a median age of 60 years old and a heavy smoking history [2, 5]. LCNEC are usually peripheral tumours and less frequently centrally located [8]. They intend to have irregular margins while calcification is present in about 10% of the cases as depicted in a CT imaging review [29]. Chest pain is the most frequent symptom along with hemoptysis, dyspnea, cough, flu-like symptoms and weight loss, while up to 24% of the patients seem to be asymptomatic at the time of diagnosis [30]. Paraneoplastic symptoms are absent with the

rare exception of a single case of syndrome of inappropriate antidiuretic hormone secretion (SIADH) [20, 31].

Diagnosis

Large-cell neuroendocrine carcinoma is very difficult to diagnose and usually is under-diagnosed [32]. Diagnosis is difficult to be set on small biopsies or cytology because the neuroendocrine pattern and differentiation is difficult to be identified in small tissue samples. Also, LCNECs are frequently located out of reach of fiberoptic bronchoscopy, so no biopsy can be obtained. The diagnosis of LCNEC requires surgical lung biopsy to be safe [2, 33].

Prognosis

LCNECs are biologically aggressive cancers and present many similarities not only in molecular level but also in overall prognosis to small–cell lung cancers manifesting a poor outcome as depicted by Asamura et al. with a 5-year survival rate at about 40,3% with the histologic grade being the most important prognostic factor [34]. In another study Garcia – Yuste et al. presented a 5-year survival rate of LCNEC patients at about 21% while for SCLC patients 14%, much lower than for patients for typical and atypical carcinoids or other non-small cell lung cancers [20]. Moreover, at a large study conducted by

Battafarano et al. in over 2000 surgically treated patients the 5-year survival rate for stage I LCNEC was only 32,1% [35].

Previously, we have depicted the role of several molecular markers in prognosis of LCNEC. Most recently the role of nestin, a class VI intermediate filament protein expressed in stem-cells during central nervous system development, was studied in patients with resected LCNECs. According to the study, nestin expression seemed to be an indicator of poor prognosis in those patients [36].

Treatment

1. Treatment of early stage disease

The therapeutic strategy is based on the extension of the disease, although the truth is that the optimal treatment for LCNEC is unknown. Due to the fact that is a relative uncommon malignancy, large prospective randomized face III trials have not been performed [37].

Most of the patients with localized early stage disease are surgically treated usually undergoing lobectomy or pneumonectomy since they may improve survival if there are no indications of lymph node metastasis at mediastinal sampling [30]. Unfortunately, even in stage I LCNEC are rarely cured [30, 35, 38]. Veronese et al. in a retrospective analysis of 144 surgical cases showed a survival benefit for patients with stage I LCNEC who had received neo-adjuvant and adjuvant

chemotherapy [39]. The same survival benefit was exhibited in a similar study conducted by Saji et al. in 2010 [40]. In both trials, platinum – based chemotherapy regimen was used in combination with etoposide or irinotecan. The same positive results in the role of adjuvant chemotherapy consisting of cisplatin and VP-16 was shown in a prospective study conducted by Iyoda et al. with a five year survival rate of 88,9% [41]. Lastly, in 2011 Sarkaria et al. depicted a trend toward improved overall survival (median survival 7,4 vs 2 years) for stages IB-IIIA LCNEC patients who had received platinum based induction or adjuvant chemotherapy [42]. Although it seems to be helpful, there are no sufficient data to support a definite role for radiation in adjuvant therapy [43].

From the above it is evident that for early-stage LCNEC patients a combination of surgery and chemotherapy regimens similar to those administered in small- cell lung cancer therapy is the preferred option.

2. Treatment of advanced disease

There is very little information about the treatment of unresectable and advanced LCNEC. In a study conducted by Igawa et al. in 2010, 14 patients with high-grade non-small cell neuroendocrine carcinoma (HNSCNEC) were treated with platinum-based regimens and compared with patients who received chemotherapy for extensive disease small- cell

lung cancer, with a comparable clinical efficacy (Median survival time 10 and 12, 3 months respectively) [44].

Five years before that in 2005 Yamazaki et al. suggested that the response rate of patients with LCNEC treated with cisplatin-based chemotherapy was comparable to SCLC [45]. Recently tumor specimens and clinical reports of 45 patients diagnosed with advanced LCNEC were reviewed. They were divided into "SCLC" and "NSCLC" regimen groups according to the first-line chemotherapeutic regimens. The response rates were 73% and 50% respectively and the difference in overall survival was 7,3 vs 9,2 months. There was also notable difference in the type and efficacy of salvage chemotherapy between the two groups, with relatively high objective responses in the "SCLC" regimen group contrary to no objective response in "NSCLC" regimen group [46].

Interestingly in full contrast to the above findings, the last updated National Comprehensive Cancer Network (NCCN) Guidelines recommend to treat LCNEC such as non small cell lung cancer [47]. Lastly, according to the results of a most recent multicenter prospective face II study, the outcomes of patients with advanced LCNEC treated with cisplatin etoposide doublets are poor and similar to those of patients with advanced SCLC [48].

The role of radiation therapy in advanced stage LCNEC remains hazy and undefined [21].

3. Targeted therapies

In the section of molecular markers we have depicted the potential role of some of those markers for future targeted therapies. A face II study evaluated the activity of sunitinib in patients with advance neuroendocrine tumours. Further trials should define its role in this matter [49]. Moreover a combination of octreotide and oral everolimus was used in a face II study in patients with neuroendocrine tumours. Progression - free survival was 13,6 vs 5,6 months for the placebo plus octreotide LAR arm. Further studies are needed to clarify the population more likely to respond to this therapy [50].

Conclusion

LCNEC is a distinct subset of pulmonary neuroendocrine tumours which histologicaly shares features of both NSCLC and SCLC. It is an uncommon but aggressive in terms of biological behaviour neoplasm with a poor prognosis and survival similar to that of small-cell lung cancer. Diagnosis is very difficult and the best therapeutic approach is still unclear. Early diagnosis followed by surgery and adjuvant platinum-based chemotherapy is the best approach. Further large scale phase III prospective studies are needed to clarify matters on this subject.

STUDY OF 19 PATIENTS WITH LARGE - CELL NEUROENDOCRINE TUMORS OF THE LUNG. A SINGLE ONCOLOGY DEPARTMENT EXPERIENCE.

Abstract

Introduction: Large-cell neuroendocrine carcinoma (LCNEC) is a pulmonary neuroendocrine tumor with poor prognosis and no established treatment.

The aim of the study was to present clinical characteristics and treatment results of patients with LCNEC.

Patients: In our department 19 LCNEC patients (m/f =14/5, 04/1997-01/2013), were consecutively treated. Clinical characteristics, treatment results and histological specimens were reviewed. Median (m) EFS (event-free survival) and OS (overall-survival) were calculated according to Kaplan Meier curves and log-rank test. Median age of the patients was 64 years and 13 of them had a favorable PS (0-1). Cough and chest pain were the most common presenting symptoms. Stage I- IIIA had 6, and stage IV 13 patients.

Eighteen (18) patients received chemotherapy either adjuvantly or for metastatic disease mainly with cisplatin-etoposide.

Results: Median OS for the overall population was 9,5 months (95% CI= 3,4-15,7). Median OS for early stage disease was 36,4 months vs 7,1 months for metastatic disease (p=0,057). Patients with a favorable PS had better OS than those with poor (3,3 vs 15,9 months, p<0,001). Similar findings were observed for EFS.

Conclusions: In our study the stage of the disease along with the PS of the patients played vital role in the overall outcome. Disease burden seems to have a prognostic role.

Introduction

Large-cell neuroendocrine carcinoma is a relatively rare lung tumor as it constitutes up to 3% of all lung cancers [1, 2]. It is a part of a spectrum of tumours called pulmonary neuroendocrine tumours which were first writtenly described by R. Laennec in a posthumously published report in 1831, where he was referring to an intrabronchial mass probably a bronchopulmonary carcinoid [3]. Pulmonary neuroendocrine tumors were classified into three major categories: Typical carcinoids, atypical carcinoids and small cell lung cancer until 1991, when Travis et al. described a distinct subset of tumors with prognostic spectrum similar to small cell lung cancer called large-cell neuroendocrine carcinoma [4, 5].

According to most recent knowledge, the spectrum of pulmonary neuroendocrine tumors includes tumors with neuroendocrine morphology such as the low-grade typical carcinoid (TC), the intermediate-grade atypical carcinoid (AC) and the high-grade large-cell neuroendocrine carcinoma (LCNEC) and small cell lung cancer (SCLC) [6]. They account for about 20-25% of all invasive lung cancers. Small cell lung cancer is the most frequent neuroendocrine malignancy representing 15%-20% of invasive lung cancers, while LCNEC accounts for 3% of all lung cancers [7, 8]. Large-cell neuroendocrine can be difficult to diagnose while the optimal treatment is not yet established [8].

In a retrospective study we reviewed patient's characteristics with large-cell neuroendocrine carcinoma of the lung and we assessed their treatment results and overall survival.

Materials and Methods

This study included demographic, immunohistological and disease characteristics as well as treatment results of 19 LCNEC patients who were consecutively treated in our department from April 1997 till January 2013.

Tumours were classified according to World Health Organization (WHO, 2004) [9, 10]. LCNEC were diagnosed based on the following criteria: neuroendocrine morphology with organoid nesting, trabecular pattern,

palisading and rosette-like structures, their high mitotic rate of 11 or more mitoses per 10 high-power fields, large-cell size, low nuclear to cytoplasmic ratio, the presence of large zones of necrosis and neuroendocrine differentiation manifested by immunohistochemistry [8,9,11,12]. The neuroendocrine markers used were CD56, chromogranin and synaptophysin.

Statistical Analysis

Event-free survival (EFS) was considered as the time from the date of diagnosis to the date of the disease relapse, progression after first line treatment, death from any cause or last follow-up. Overall survival (OS) was the time measured from the date of diagnosis to the date of death or last follow-up. Median survival was calculated according to the Kaplan - Meier curves, with a 95% confidence interval. Comparisons were made according to the log- rank test and hazard ratios were estimated by Cox-regression analysis. All comparisons were two-tailed and 5% was considered as the level of significance.

Results

Fourteen (14) of the patients (73, 68%) were male, while the median age of all patients was 64 years old. At the time of diagnosis 13 of the patients (68, 42%) had a favorable performance status (0-1 according to ECOG)

and 6 (31,58%) had a poor performance status (2-3 according to ECOG). Cough with dyspnea and chest pain, SVC syndrome, hoarseness, hypercalciaemia, visual disturbances, skin tumors and paradox pulse were recorded in 6,3,2,1,1,1 and 1 patient and were the most common presenting symptoms while 4 patients were asymptomatic and were randomly diagnosed.

At the time of diagnosis their disease status was as follows: 6 of them (31, 58%) had early (non- metastatic) disease stage I-IIIA and the 13 rest (68, 42%) had advanced stage IV according to the TNM System, metastatic disease. With four of them having metastasis to multiple (over 2 organs) mainly bones, liver and adrenal glands (Table 1).

Table 1.Epidimiological and clinical characteristics

Characteristics	**Total**
Median Age	*64 years*
Gender	
Male	*14*
Female	*5*
PS	
0-1 ECOG	*13*
2-3 ECOG	*6*
Stage	
I-IIIA	*6*
IV	*13*
1-2 organs	*15*
Metastasis to multiple organs	*4*

Diagnosis was set through surgery in 6 patients and through biopsy of lymph node, liver and brochonscopy in the rest. All neoplasms had neuroendocrine morphology, extensive necrosis, high mitotic rate and stained CD56, synaptophysin and chromogranin(++/+++).

With the exception of 1 patient who underwent surgery alone, the rest received chemotherapy either as adjuvant therapy or as a first line treatment for metastatic disease. The main chemotherapy regimen used in adjuvant treatment was cisplatin-etoposide. Patients with stage IV metastatic disease received as first line treatment mainly platinum based combinations with etoposide (8 /13, 61, 53%). Four patients (4/13, 30, 77%) received chemotherapy with doxorubicin, cyclophosfamide, vincristine and etoposide, while one patient received a combination of cisplatin-pemetrexed. Upon disease progression they received as salvage chemotherapy regimens used in the treatment of a small-cell lung cancer disease (Table 2 & 3).

Table 2. Treatment of patients with stage I- IIIA disease

Patients	Treatment
1st patient	*Surgery plus Cyclophosfamide– Doxorubicin-Vincristine- Etoposide (CAVE)*
2nd patient	*Surgery*
3rd patient	*Surgery plus Cisplatin/ Etoposide*
4th patient	*Surgery plus Cisplatin/ Etoposide*
5th patient	*Surgery plus Cisplatin/ Etoposide*
6th patient	*Surgery plus Cisplatin/ Docetaxel*

Table 3. Treatment of patients with stage IV metastatic disease.

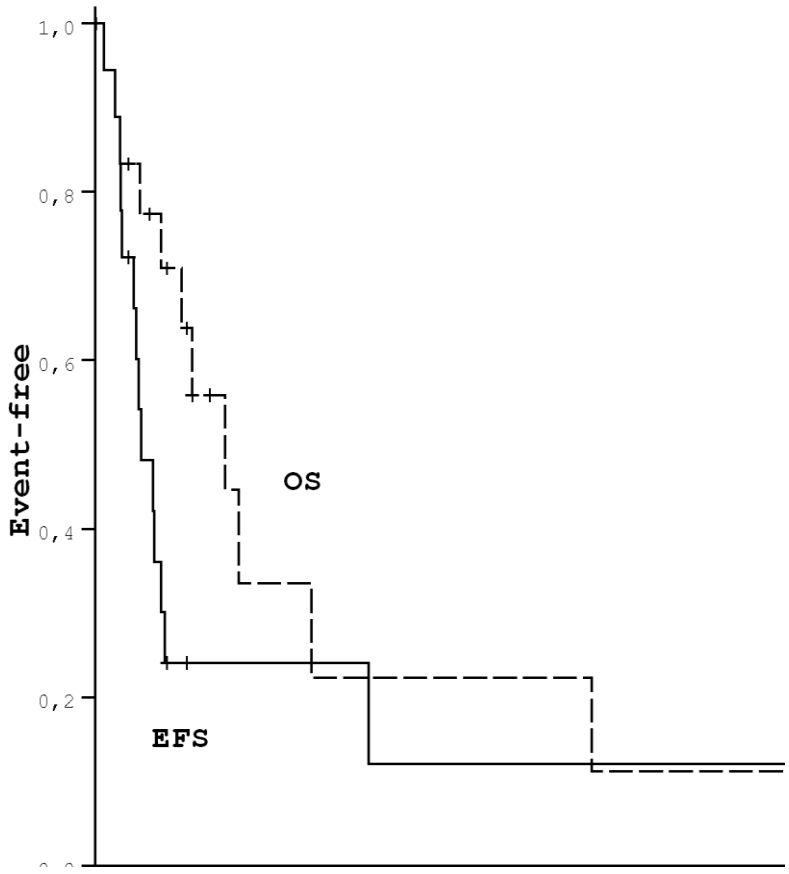
Patients	First line treatment	Second line treatment
1st patient	*RT plus CAVE*	*Cisplatin/ Etoposide*
2nd patient	*Cisplatin/ Etoposide*	*CAVE*
3rd patient	*Cisplatin/ Pemetrexed*	*Gemcitabine/ Docetaxel*
4th patient	*Cisplatin/ Etoposide*	*Hycamtin*
5th patient	*Cisplatin/ Etoposide*	-
6th patient	*RT plus Cisplatin/ Etoposide*	*CAVE*
7th patient	*RT plus CAVE*	*Cisplatin/ Etoposide*
8th patient	*CAVE*	*RT*
9th patient	*Cisplatin/ Etoposide*	-
10th patient	*RT plus CAVE*	*Hycamtin*
11th patient	*RT plus Carboplatin/ Etoposide*	*CAVE*
12th patient	*Cisplatin/Etoposide*	*CAVE plus RT*
13th patient	*Cisplatin/Etoposide*	-

Median follow-up was 8, 4 months (95% CI= 0 - 40,4 months).

Median OS for the overall population was 9,5 months (95% CI=3, 4-15,7). Patients with early (non-metastatic) disease had median OS=36,4 months versus 7,1 months for patients with metastatic disease (p =0,057). Also, patients with a favorable PS (0-1 according to ECOG) had better OS than those with poor PS (2-3), (3,3 vs 15,9 months, p<0,001). Furthermore, disease burden seemed to have a prognostic significance. Patients with multiple organs involved (>2, including the lungs) had a trend for a worse OS compared to patients with oligometastatic disease

(1-2 organs involved) and those with early disease (3,3 vs 9,5 vs 36,4 months, p= 0,068). In addition, the number of involved organs seemed to confer a worse prognosis (Hazard ratio= 1, 55, 95% CI=1, 04 - 2, 29, p=0,03).

Similar findings were observed for EFS. Median EFS for all the patients of the study was 3, 3 months (95%CI=1,7 - 4,9). Patients with early (non-metastatic) disease had median EFS=20,0 months vs 3,0 months for patients with metastatic disease (p=0,028). Also, patients with a favorable PS (0-1 according to ECOG) had better EFS than those with poor PS (2-3), (2,8 vs 4,8 months, p=0,059). However, the number of involved organs did not seem to influence EFS.



Kaplan – Meier curves depicting Median overall survival and event free survival. Confidence interval (CI) 95%.

Median overall survival 9,5 months (95% CI= 3,4 – 15,7).

Median event free survival 3,3 months (95% CI= 1,7 – 4,9).

Conclusion

The stage of the disease along with the performance status of the patients played vital role in the overall outcome and survival of the patients. Moreover disease burden seems to have a prognostic role. The findings of

our study suggest that large cell neuroendocrine tumors of the lung are biologically aggressive cancers with poor prognosis even for patients with stage I disease. These findings are consistent with those presented by Garcia-Yuste et al. with a 5-year survival rate at about 21% and to those depicted by Battafarano et al. in a study of over 2000 surgically treated patients where the 5-year survival for stage I LCNEC patients was only 32,1% [20, 35]. In our study, most of the patients with localized disease were treated by surgery plus platinum based chemotherapy in combination with etoposide which seems to be the best therapeutical approach according to at least two studies conducted by Veronese et al. in 2006 and Sagi et al. in 2010 [40, 41]. Further large scale phase III prospective studies are needed to clarify the best therapeutic approach for this aggressive pulmonary neuroendocrine tumor.

REFERENCES

[1] Franklin WR, Chanin T, Gonzalez A. Molecular and cellular pathology of lung cancer. In: Pass HI, et al., editors. Lung cancer principles and practice. Philadelphia: Lippincott, Williams and Wilkins; 2005. p. 231–60.

[2] Travis WD, Krug LM, Rusch V. Large cell neuroendocrine carcinoma. In: Raghavan D, et al., editors. Textbook of uncommon cancer. New York: John Wiley & Sons; 2006. p. 298–306.

[3] Laennec R. Traite de l'auscultation mediate et des maladies des poumons et du coeur. Paris: Me´riadec Lae¨nnec; 1831.

[4] Moran CA, Suster S, Coppola D, et al. Neuroendocrine carcinomas of the lung: a critical analysis. Am J Clin Pathol 2009; 131:206–21.

[5] Travis WD, Linnoila RI, Tsokos MG, et al. Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma: an ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. Am J Surg Pathol. 1991; 15:529-553.

[6] Travis WD. Lung tumours with neuroendocrine differentiation. Eur J Cancer 2009; 45 (Suppl 1): 251–266.

[7] Travis WD, Travis LB, Devesa SS. Lung cancer. Cancer 1995; 75: 191–202 [published erratum appears in Cancer 1995; 75: 2979].

[8] Chen LC, Travis WD, Krug LM. Pulmonary neuroendocrine tumors: what (little) do we know? J Natl Compr Canc Netw 2006; 4: 623–630.

[9] Travis WD, Brambilla E, Muller-Hermelink HK et al. Pathology and Genetics: Tumours of the Lung, Pleura, Thymus and Heart. Lyon: IARC 2004.

[10] Travis WD, Colby TV, Corrin B et al. Histological Typing of Lung and Pleural Tumors. Berlin: Springer; 1999.

[11] Travis, W. D. "Advances in neuroendocrine lung tumors." Annals of Oncology 21.suppl 7 (2010): vii65-vii71.

[12] Travis WD, Rush W, Flieder DB et al. Survival analysis of 200 pulmonary neuroendocrine tumors with clarification of criteria for atypical carcinoid and its separation from typical carcinoid. Am J Surg Pathol 1998; 22: 934–944.

[13] Jiang SX, Kameya T, Shoji M, et al. Large cell neuroendocrine carcinoma of the lung: a histologic and immunohistochemical study of 22 cases.AmJ Surg Pathol 1998; 22:526–37.

[14] Folpe AL, Gown AM, Lamps LW et al. Thyroid transcription factor-1: immunohistochemical evaluation in pulmonary neuroendocrine tumors. Mod Pathol 1999; 12: 5–8.

[15] Sturm N, Rossi G, Lantuejoul S et al. Expression of thyroid transcription factor-1 in the spectrum of neuroendocrine cell lung proliferations with special interest in carcinoids. Hum Pathol 2002; 33: 175–182.

[16] Iyoda A, Hiroshima K, Moriya Y, et al. Pulmonary large cell neuroendocrine carcinoma demonstrates high proliferative activity. Ann Thorac Surg 2004; 77:1891–5.

[17] Onuki N, Wistuba II, Travis WD, et al. Genetic changes in the spectrum of neuroendocrine lung tumors. Cancer. 1999; 85:600–607.

[18] Murakami I, Fujiwara Y, Yamaoka N, et al. Detection of p53 gene mutations in cytopathology and biopsy specimens from patients with lung cancer. Am J Respir Crit Care Med. 1996; 154(4 Pt 1):1117–1123.

[19] Zaffaroni N, De Polo D, Villa R, et al. Differential expression of telomerase activity in neuroendocrine lung tumors: correlation with gene product immunophenotyping. J Pathol 2003; 201:127–33.

[20] Garcia-Yuste, Matilla JM, Alvarez-Gago T, et al. Prognostic factors in neuroendocrine lung tumors: a Spanish multicenter study. Ann Thorac Surg 2000; 70:258–63.

[21] Rossi G, Cavazza A, Marchioni A, et al. Role of chemotherapy and the receptor tyrosine kinases KIT, PDGFRalpha, PDGFRbeta, and MET

in large-cell neuroendocrine carcinoma of the lung. J Clin Oncol 2005; 23:8774–85.

[22] Takeichi M. Cadherin cell adhesion receptors as a morphogenetic regulator. Science. 1991; 251:1451–1455.

[23] Pelosi G, Scarpa A, Puppa G, et al. Alteration of the E-cadherin/ beta-catenin cell adhesion system is common in pulmonary neuroendocrine tumors and is an independent predictor of lymph node metastasis in atypical carcinoids. Cancer. 2005;103:1154–1164.

[24] Takano T, Fukui T, Ohe Y, Tsuta K, Yamamoto S, Nokihara H, Yamamoto N, Sekine I, Kunitoh H, Furuta K and Tamura T: EGFR mutations predict survival benefit from gefitinib in patients with advanced lung adenocarcinoma: a historical comparison of patients treated before and after gefitinib approval in Japan. J Clin Oncol 26: 2008; 5589-5595.

[25] Iyoda, Akira, et al. "Expression profiling and identification of potential molecular targets for therapy in pulmonary large-cell neuroendocrine carcinoma." Experimental and Therapeutic Medicine 2.6 (2011): 1041.

[26] Yanagisawa, S., Morikawa, N., Kimura, Y., Nagano, Y., Murakami, K. and Tabata, T., Large-cell neuroendocrine carcinoma with epidermal growth factor receptor mutation: Possible transformation of lung adenocarcinoma. Respirology 2012; 17: 1275–1277.

[27] De Pas TM, Giovannini M., et al., large – cell neuroendocrine carcinoma of the lung harboring EGFR mutation and responding to gefitinib. J Clin Oncol, 2011; Dec.; 29(34): e 819-822.

[28] Odate S., Nakamura K., Onishi H., Kojima M., Uchiyama A., Nakano K, Kato M., Tanaka M., Katano M., TrkB/BDNF signaling pathway is a potential therapeutic target for pulmonary large cell neuroendocrine carcinoma. Lung Cancer 2013; 79 (3), pp. 205-214.

[29] Akata S, Okada S, Maeda J, et al. Computed tomographic findings of large cell neuroendocrine carcinoma of the lung. Clin Imaging 2007; 31: 379–84.

[30] Zacharias J, Nicholson AG, Ladas GP et al. Large cell neuroendocrine carcinoma and large cell carcinomas with

neuroendocrine morphology of the lung: prognosis after complete resection and systematic nodal dissection. Ann Thorac Surg 2003; 75: 348–352.

[31] Oh HJ, Lee MJ, Jang SJ, Shin DH, Kang SW. Syndrome of inappropriate antidiuretic hormone secretion in a patient with large cell neuroendocrine carcinoma. Yonsei Med J. 2012 May; 53(3):667-9. doi: 10.3349/ymj.2012.53.3.667.

[32] Takei H, Asamura H, Maeshima A, et al. Large cell neuroendocrine carcinoma of the lung: a clinicopathologic study of eighty seven cases. J Thorac Cardiovasc Surg 2002; 124:285–92.

[33] Hiroshima K, Abe S, Ebihara Y et al. Cytological characteristics of pulmonary large cell neuroendocrine carcinoma. Lung Cancer 2005; 48: 331–337.

[34] Asamura H, Kameyo T, Matsuno Y, et al. Neuroendocrine neoplasms of the lung: a prognostic spectrum. J Clin Oncol 2006; 24:70–6.

[35] Battafarano R, Fernandez F, Ritter J, et al. Large cell neuroendocrine carcinoma: an aggressive form of non-small lung cancer. J Thorac Cardiovasc Surg 2005; 130:166–72.

[36] Ryuge S., Sato Y.,Jiang S.X., Wang G., Matsumoto T., Katono K., Inoue H, (...) Masuda N. Prognostic impact of nestin expression in resected large cell neuroendocrine carcinoma of the lung (2012). Lung Cancer; 77 (2), pp. 415-420.

[37] Gridelli C., Rossi A., Airoma G., Bianco R., Costanzo R., Daniele B., Chiara G.D., Grimaldi G., Irtelli L., Maione P., et al. Treatment of pulmonary neuroendocrine tumours: State of the art and future developments. Cancer Treat. Rev. 2012 .10.1016/j.ctrv.2012.06.012.

[38] Cooper WA, Thourani VH, Gal AA, et al. The surgical spectrum of pulmonary neuroendocrine neoplasm. Chest. 2001;119:14–18.

[39] Veronesi G, Morandi U, Alloisio M, et al. Large cell neuroendocrine carcinoma of the lung: a retrospective analysis of 144 surgical cases. Lung Cancer. 2006; 53:111–115.

[40] Saji H, Tsuboi M, Matsubayashi J, et al. Clinical response of large cell neuroendocrine carcinoma of the lung to perioperative adjuvant chemotherapy. Anticancer Drugs. 2010; 21:89–93.

[41] Iyoda A, Hiroshima K, Moriya Y, et al. Postoperative recurrence and the role of adjuvant chemotherapy in patients with pulmonary large cell carcinoma. J Thorac Cardiovasc Surg. 2009; 132:446–453.

[42] Sarkaria IS, Iyoda A, Roh MS, Sica G, Kuk D, Sima CS, et al. Neoadjuvant and adjuvant chemotherapy in resected pulmonary large cell neuroendocrine carcinomas: a single institution experience. Ann Thorac Surg. 2011; 92:1180–1186.

[43] Mackley HB, Videtic GM. Primary carcinoid tumors of the lung: a role for radiotherapy. Oncology (Williston Park). 2006; 20:1537–1543.

[44] Igawa S, Watanabe R, Ito I, Murakami H, Takahashi T, Nakamura Y, Tsuya A, Kaira K, Naito T, Endo M, Yamamoto N, & Kameya T. Comparison of chemotherapy for unresectable pulmonary high-grade non-small cell neuroendocrine carcinoma and small-cell lung cancer. Lung Cancer 2010 Jun; 68(3):438-45.

[45] Yamazaki S, Sekine I, Matsuno Y, et al. Clinical responses of large cell neuroendocrine carcinoma of the lung to cisplatin based chemotherapy. Lung Cancer 2005; 49:217–23.

[46] Sun, J. M., Ahn, M. J., Ahn, J. S., Um, S. W., Kim, H., Kim, H. K., ... & Park, K. Chemotherapy for pulmonary large cell neuroendocrine carcinoma: Similar to that for small cell lung cancer or non-small cell lung cancer?. Lung Cancer; 2012.

[47] NCCN, Clinical Practice Guidelines in Oncology – Small cell lung cancer. Version 2 - 2013.

[48] Le Treut, J., Sault, M. C., Lena, H., Souquet, P. J., Vergnenegre, A., Le Caer, H., ... & Chouaid, C. Multicentre phase II study of cisplatin–etoposide chemotherapy for advanced large-cell neuroendocrine lung carcinoma: the GFPC 0302 study. Annals of Oncology; 2013.

[49] Kulke MH, Lenz HJ, Meropol NJ, et al. Activity of sunitinib in patients with advanced neuroendocrine tumors. J Clin Oncol. 2008; 26:3403–3410.

[50] Pavel ME, Hainsworth JD, Baudin E, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet. 2011; 378:2005–2012.