Research Article

INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH

ISSN: 2395-6429, Impact Factor: SJIF: 4.656
Available Online at www.journalcmpr.com
Volume 4; Issue 2(B); February2018; Page No. 3029-3033
DOI: http://dx.doi.org/10.24327/23956429.ijcmpr20180391

SMALL CELL LUNG CANCER : A RETROSPECTIVE TUNISIAN STUDY ABOUT 70 CASES AND A REVIEW OF LITERATURE

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ARTICLE INFO

Article History:
Received 20th November, 2017
Received in revised form 8th December, 2017
Accepted 3rd January, 2018
Published online 28th February, 2018

Key words:
small cell lung cancer, radiochemotherapy, palliative chemotherapy.

ABSTRACT

Background: Small-cell lung carcinoma (SCLC) is an aggressive form of lung cancer. Therapeutic strategies are chemotherapy (CT), radiotherapy (RT) and supportive care. The objective of our study was to investigate the epidemiologoical and clinicopathologic characteristics, therapy methods and prognosis of SCLC.

Methods: We conducted a retrospective study of 70 cases of SCLC collected in the department of medical oncology of Salah Azaiz institute in Tunis over a period of 6 years (2010-2015).

Results: The study population comprised 66 men and 4 women. The mean age was 58 years [34-88]. All patients were smokers. At presentation, the vast majority of patients were symptomatic. Pathological diagnosis was obtained essentially by the performance of bronchoscopic biopsy. It revealed a lung small cell neuroendocrine carcinoma. Fifty percent of tumors were immunoreactive for TTF-1, 90% for keratin and 73% for EMA. Tumors cells stained positively for markers of neuroendocrine differentiation including chromogranin A, synaptophysin and CD56. The disease was metastatic in 75% of cases. According to the VALCSG classification, the tumor was staged as limited-stage disease in 15 cases and extensive-stage disease in 55 cases. Thirteen patients received a curative –intent CT : 10 patients had induction CT before RT and 3 patients had concomitant radio-chemotherapy (RCT). Etoposide with cisplatin (EP) was the used regimen. The median overall survival (OS) in the limited-stage disease (LD) group was 16 months and the median progression free survival (PFS) was 13 months. Eighty two percent of patients with extensive-stage disease(ED) received palliative chemotherapy. The main regimens were EP, etoposide with carboplatin and CAV (cyclophosphamide, doxorubicin and vincristine). Seventeen patients received second line CT. Only 6 patients had third- line CT. A whole brain RT, thoracic RT, analgesic RT and RT of spinal cord compression were administrated in 35%, 28%, 11 % and 6% of cases, respectively. The median OS in this group was 9 months and the median progression free survival was 4 months. Ninety one percent of patients received morphine. Thirty percent of patients were oxygen dependent. Evacuative thoracentesis was performed in 24 % of cases. The median overall survival of the study population was 10.32 months.

Conclusion: Small cell lung cancer has poor prognosis. Developing prognosis biomarkers and experimenting new agents are needed to improve outcomes.

INTRODUCTION

Small-cell lung carcinoma (SCLC) accounts for 20% to 25% of all new cases of lung cancer [1]. It is categorized as high-grade neuroendocrine carcinoma. SCLC is distinguished by high malignancy, short doubling time, early and extensive metastasis, good response to initial chemotherapy and radiotherapy but easy development of secondary drug resistance and relapse. It is associated with poor survival. Initially most patients present with metastases .Only 30% to 40% of patients present with limited-stage SCLC at the time of diagnosis [2]. Limited disease (LD) patients can achieve a median survival of 15-20 months while extensive disease (ED) patients have a median survival of 8–13 months [3].In this study, we retrospectively analyzed epidemiological and clinicopathological characteristics, therapy modalities and outcomes in 70 cases of SCLC.

MATERIALS AND METHODS

Seventy patients were included in the study with histologically confirmed SCLC treated in the department of medicaloncology at Salah Azaiz Institute in Tunis, Tunisia from January 2010 to December 2015. The pathological diagnosis was obtained by the performance of bronchoscopic biopsy, computed tomography (CT) guided percutaneous biopsy, surgical biopsy

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and mediastinoscopy in 61.1%, 21.4%,14.3% and 3% of cases, respectively. Brain and thoraco-abdominopelvic CT scan was performed on all patients. Three patients (4.3%) had a brain MRI. Bone scan was performed on 39 patients (55.7%). The bronchoscopy was realized in 77.1% of cases. Disease was classified according to the staging criteria by Veterans Administration Lung Study Group (VALG). Objective tumor response after radiotherapy and chemotherapy was evaluated according to response evaluation criteria in solid tumours (RECIST) guidelines (version 1.1). The overall survival time was calculated from the date of diagnosis to death or to the last follow-up date. Progression free survival (PFS) was calculated from the first day of treatment and the date on which disease progressed or the date on which the patient died .Statistical analyses were carried out with the SPSS version 20. Overall survival and PFS rates were estimated using the Kaplan–Meier method and compared with the log-rank tests. The level of statistical significance was set at a P-value of 0.05.

RESULTS

Epidemiological and clinical characteristics of patients are shown in **table 1.**

Table 1 Epidemiological and clinical characteristics of patients

Characteritics Overall patients	(N=70)	%
Gender		
Male	66	94.3
Female	4	5.7
Age		
Mean age (range,years)	58 (34-88)	
Smoking status		
Yes	70	100
No	0	0
Cigarette consumption		
Mean concumption (range,pack-years)	56.1 (20-90)	
Functional signs		
Thoracic pain	35	50.7
Deterioration of the general status	33	47.7
Cough	25	35.7
Hemoptysis	19	27.1
Dyspnea	18	25.7
Neurological signs	12	17.1
Superior vena cava syndrome	10	14.3
Consultation period		
Median period (range ,months)	3 (1-12)	
Performance status		
0	6	8
1	20	28
2	34	49
3	8	12
4	2	3
Paraneoplasic syndrome		
Digital clubbing	6	10
Peripheral neuropathy	1	1.4

Bronchial biopsy was done in 60% of cases, lymph node biopsy in 18 % , biopsy of a pulmonary nodule or mass in 16%,pleural biopsy in 3% and biopsy of metastatic lesion (liver and brain) in 3% of cases. The pathological diagnosis revealed a lung small cell neuroendocrine carcinoma. Immunohistochemestry study was performed on 53% of patients. Fifty percent of tumors were immunoreactive for Thyroid transcription factor 1 (TTF-1), 90% for keratin and 73% for EMA (epithelial membrane antigen). Tumors cells stained positively for markers of neuroendocrine differentiation including chromogranin A, synaptophysin and neural cell adhesion molecule (CD56, NCAM) in 90%, 90% and 73% of the cases, respectively. The mean tumor size was 66.58 mm [7-150]. The tumor was proximal in 54%, intermediate in 10. 6% and peripheral in 7.6% of patients. The tumor site was lobar in 71%, mediastinal in 25% and hilar in 15% of cases. The right lung was the most affected (65%).

All patients had lymph node involvement. At diagnosis date, the disease was metastatic in 75.5% of cases. The main sites of metastases were brain, bone, adrenal gland, lung, pleura, liver and pancreas in 37%, 35%, 30%,26%,26%,22% and 7% of the cases, respectively . According to the VALCSG classification, the disease was limited-stage (LD) in 15 cases (21%) and extensive-stage (ED) in 55 cases (79%). Eleven patients (15.7%) didn't receive any chemotherapy (CT) nor radiotherapy (RT) because of death, poor physical condition or loss to follow up. Median treatment initiation time was 2 weeks [1-3weeks]. In the LD group, 13 patients had a therapy with curative intent . Ten patients had induction chemotherapy (IC) and programmed to have thoracic RT and 3 patients had concomitant radio-chemotherapy (RCT). One patient was lost to follow-up and one patient didn't receive treatment because of poor physical condition.

Regimen of induction chemotherapy was etoposide and cisplatin (EP). The main toxicity was digestive (vomiting, epigastralgia). Partial response was obtained in 4 cases, complete response in 2 cases, progression in 3 cases and stability in one case. Six patients among those who had induction chemotherapy had a thoracic irradiation (sequential RCT). The main toxicity of RT was dysphagia and dysphonia (grade 2). Two patients had prophylactic brain irradiation and 2 patients received palliative thoracic radiotherapy. A first line chemotherapy was administered in 2 patients (EP and CAV:cyclophosphamide1 g/m² day1, doxorubicin 50mg/m² day 1 and vincristine 1.4mg/m² day1 every 21 days). Three patients received concomitant RCT. These regimens were well tolerated. The response was progression in 2 cases and complete response in 1 case. In second intention, 2 patients received the protocol CAV with progression during treatment. Overall survival was better in the sequential RCT group versus concomitant RCT group but without a statistical significance (24 vs 12 months, p=0.364) Regimens of induction chemotherapy followed by thoracic RT and concomitant radiochemotherapy are shown in **table 2**.Objective responses in LD group are shown in **table 3**.

Table 2 Regimens of induction chemotherapy followed by thoracic RT and concomitant RCT

Strategy	Induction chemotherapy followed by RT	Concomitant RCT
Chemotherapy	Etoposide:100 mg/m² days 1,2,3 and Cisplatin 80 mg/m² day 1 (every 21 days) median dose : 42 Gy [26-60Gy]	2 cycles of EP then 2 cycles of EP(with reduced dose) in concomitant with RT then 2 cycles of EP
Radiotherapy	3D conformal median dose 42 Gy [26-60Gy] The target volume should be defined based on the pretreatment CT scan Fractionation :2.0 Gy once daily, 5 times a week	3D conformal median dose 46 Gy [44-50 Gy] The Target volume :should be defined based on the pretreatment CT scan Fractionation :2.0 Gy once daily, 5 times a week

Survival outcomes in the LD group are detailed in table 4. In extensive disease group, 10 patients underwent supportive care because of poor general status. Eighty two percent of patients received palliative chemotherapy. The main regimens were EP, etoposide with carboplatin (AUC5) and CAV in 84%, 11 % and 4 % of cases, respectively. The median number of cycles was 4 [1-8]. The main toxicities were digestive, neutropenia, renal and anemia in 22%, 13%, 6% and 4% of cases, respectively. Dose reduction was done in 13 % of cases.

There was no difference of overall survival between carboplatine containing regimens and cisplatine containg regimens (10.89 months vs 9 months, p=0.637). Objective responses are summarized in table 3. Seventeen patients received second line chemotherapy. Chemotherapy regimens were CAV in 64 % of cases, etoposide and cisplatin in 18%, etoposide and carboplatin in 5%, paclitaxel in 5% and gemcitabine and cisplatine in 5% of cases. A progression was recorded in all patients. Only 6 patients had third- line chemotherapy (cav, campto, campto cisplatin, weekly paclitaxel and vinorelbin cisplatin) with progression disease. In extensive- stage disease group,a whole brain radiotherapy was administered in 35% of patients with brain metastases (30 Gy in 10 daily fraction). Thoracic RT was administered in 28% of patients, analgesic RT in 11 % of patients and spinal cord RT in 6% of patients. Survival outcomes in the ED group are summarized in table 4.

Median survival of SCLC with brain metastases was 8.15 months (5.42-10.87) versus 9.62 months (6.93-12.32) with others metastases (p=0.529). Sixty five percent of the study population were algic Ninety percent of patients received grade 3 analgesics. Thirty percent of patients were oxygen dependent. Evacuative thoracentesis was performed in 24 %of cases. Smoking cessation was recorded at 30% of patients. The median overall survival of the study population was 10.32 months (1-72 months). The OS was better in the limited-stage disease group (p=0.065). The PFS is also better in the same group (p<0.001). Comparison of overall survival and progression free survival between patients with local disease and extensive-stage SCLC are shown respectively in figure 1 and 2.

Table 3 Objective responses

Clinical response	Limited -stage disease (n,%)	Extensive-stage disease (n,%)
Complete response	3 (23%)	1(2%)
Partial response	4 (31%)	6 (13%)
Stable disease	1(8%)	7(15%)
Progressive disease	5 (38%)	31(70%)

Table 4 Survival outcomes

Survival	Limited stage disease (LD)	Extensive stage disease (ED)
Progression free survival Median (months ,range)	13 months [3.6-22.6]	4 months [3.1-4.8]
Overall survival Median (months ,range)	16 months [2-72]	9 months [1-24]
One year OS rate	50%	35%
Two year OS rate	14%	1.8%

DISCUSSION

Small-cell lung carcinoma (SCLC) accounts for 20% to 25% of all new cases of lung cancer [1].Of the various histologic types of lung cancer, small-cell lung cancer is the most

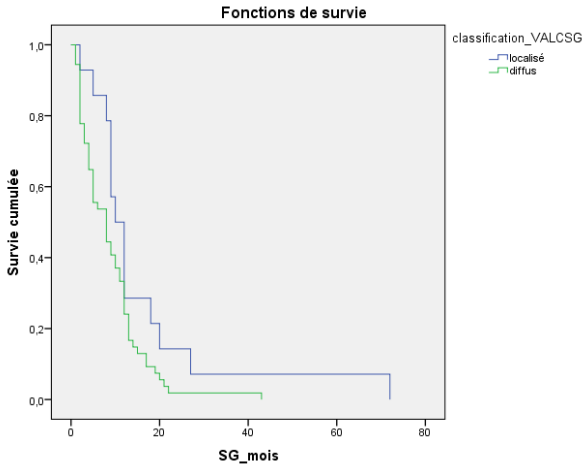

Figure 1 Comparison of OS between patients with limited stage disease and extensive-stage disease

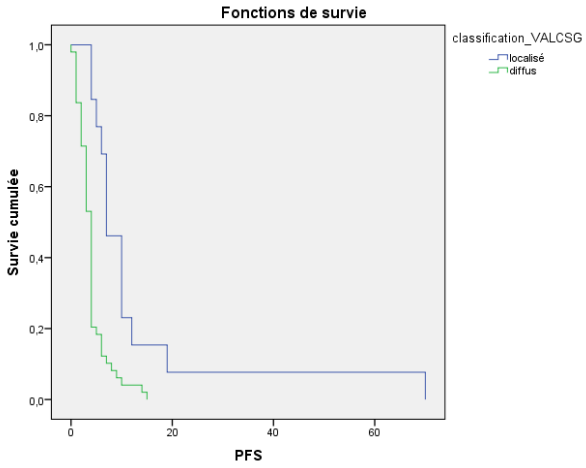

Figure 2 Comparison of PFS between patients with limited stage disease and extensive-stage disease

sensitive to chemotherapy and radiotherapy, yet overall outcome is poor. Cigarette smoking remains the major cause of SCLC, and nearly all cases of SCLC are attributable to tobacco use [4]. The recent increase in SCLC in women is associated with a rise in cigarette smoking among women over the past two to three decades. Currently, no effective screening test is available to detect early-stage SCLC [5].The disease is typically diagnoses when it becomes symptomatic. Main symptoms are weight loss, dyspnea, cough, bone pain and neurological signs. Many neurological (e.g Lambert-Eaton myasthenic syndrome, sensory neuropathy) and endocrine (eg syndrome of inappropriate ADH secretion, Cushing syndrome) paraneoplastic syndromes are associated with SCLC [6].

Typical SCLC is characterized by hyperchromatic nuclei with a very high nucleus to cytoplasm ratio; a diffuse, finely stippled pattern of chromatin; and indistinct nucleoli. The cells are small, approximately two to three times the size of a lymphocyte. Nearly all SCLCs are immunoreactive for keratin, epithelial membrane antigen(EMA), and thyroid transcription factor-1 (TTF-1). Most SCLCs stain positively for markers of neuroendocrine differentiation including chromogranin A, neuron-specific enolase (NSE),neural cell adhesion molecule (NCAM,CD56) and synaptophysin [7].

Complete staging should include history and physical examination, thoracoabdominopelvic CT scan and brain imaging (CT scan or preferentially MRI) [8]. Because of the

aggressive nature of SCLC, staging should not delay the onset of treatment .In our study median treatment initiation time was 2 weeks [1-3 weeks]. The VA Lung Study Group's 2-classification (VALSGC) is used to define the extent of disease in patient with SCLC. Limited –stage disease is disease confined to the ipsilateral hemithorax which can be safely encompassed within a radiation field and extensive –stage disease is disease beyond the ipsilateral hemithorax, including malignant pleural or pericardial effusion or hemtaogenous metastases [9]. The most studied prognostic factors in SCLC were poor performance status (3-4) ,extensive –stage disease and weight loss [10].

Approximately two thirds of patients with SCLC present with extensive disease and most of those with apparently localized disease are presumed to have occult metastatic involvement that's why SCLC is regarded as a systemic disease [2]. In our study, we had more extensive-stage disease (79%). Treatment for patients with limited-stage SCLC and good PS(0-2) consists of chemotherapy with concurrent thoracic radiotherapy. For patients with extensive-stage disease chemotherapy alone is the recommended treatment. Radiotherapy may be used for palliation of symptoms [11-12].

Etoposide and cisplatin (EP) is the most commonly used combination chemotherapy regimen and constitutes the standard regimen of limited-stage and extensive -stage SCLC [13]. In our study, EP represented 100 % of regimens in LD group and 84% of regimens in ED group. Cisplatin could be remplaced by carboplatin to reduce essentially the risk of nephropathy. A meta-analysis including 663 patients (62% ED and 38% LD) and comparing cisplatin versus carboplatin showed equivalent efficacy(response rate 67% vs 66% ,progression free-survival 5.5 vs 5.3 months and overall survival 9.6 vs 9.4 months) [14].Our results were consistent with literature. Many regimens are studied in order to improve outcomes of etoposide and cisplatin chemotherapy. The combination of irinotecan and cisplatin or irinotecan carboplatin is an option of EP but its superiority to EP remains controversial [15-16].

A three-drug regimens are also tested in the hope of improving survival outcomes. The addition of ifosfamide (or cycophosphamide and anthracycline) to EP showed a modest survival benefit in extensive disease but induced considerable toxicity [17]. The addition of paclitaxel to either cisplatin or carboplatin and etoposide dosen't improve survival [18]. The use of maintenance or consolidation chemotherapy beyond 4-6 cycles increased toxicity but not survival [19].

Although SCLC is very responsive to initial treatment, most patients relapse. Subsequent chemotherapy generally involves single -agent therapy. Active subsequent agents include paclitaxel, docetaxel, irinotecan, topotecan, vinorelbine, gemcitabine and ifosfamide. The CAV regimen and topotecan had similar results. Survival results are still disappointing [20]. The benefits of antiangiogenic therapy (eg bevacizumab) are being evaluated in SCLC and not yet demonstrated [21].

In limited-stage disease ,The addition of thoracic radiotherapy improved local control by 25% and is associated with small but significant improvement in survival according to a meta-analyses including more than 2000 patients [22].

Early concurrent radiotherapy results in improvement of local and systemic control and overall survival when compared with late concurrent or sequential radiotherapy [23]. In our study 3 patients had concomitant radiochemotherapy and 6 patients had sequential RCT .Overall survival is better in the sequential RT group but without statistical significance (p=0.364).This result could be explained by the 72 month-overall survival of a patient with LD and who received sequential RCT. Previous reported experiences showed that in the context of a disease with a very poor prognosis, there exists a small group of patients with a surprisingly long survival. Prognostic and predictive factors are still unknown [24].

Prophylactic cranial irradiation (PCI) decreases the incidence of brain metastases.PCI is recommended for patients with either limited or extensive -stage disease who attain a partial or complete response. For patients with symptomatic disease (bone pain, spinal cord compression, obstructive atelectasis,) or with brain metastases, radiotherapy can offer excellent palliation. Median survival rates are only 15 to 20 months for limited-stage disease and 8 to 13 months for extensive- stage disease [3]. In our study, survival rates are similar to others reported in the literature.

CONCLUSION

Small cell lung cancer is still associated with poor prognosis. Efforts to reduce mortality of SCLC should instead focus on prevention through tobacco reduction programs, as well as the development of improved treatment options and prognosis biomarkers.

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How to cite this article:

Berrazaga Y *et al* (2018) 'Small Cell Lung Cancer: A Retrospective Tunisian Study About 70 Cases And A Review Of Literature', *International Journal of Current Medical and Pharmaceutical Research,* 4(2), pp. 3029-3033.

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