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Small Cell Lung Cancer in Good Performance Status: A Mono-Center Tunisian Study

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Abstract

Background: Small cell lung cancer (SCLC) accounts for 20% of lung cancers with aggressive presentation. Therapies for SCLC have lagged behind the current standard treatment, the prevailing state-of-the-art from the early 1980s. The aim of this study is to report the epidemiological, clinical profile, therapeutic protocols, and results of SCLC in Tunisian population.
Methods: This is a retrospective study, including 60 patients treated for histologically diagnosed with SCLC between 2011 and 2015. Only patients with eastern cooperative oncology group (ECOG) performance status 0 to 2 were considered.
Results: Sixty patients were enrolled in this study. The mean age was 61.8 years (range 45 - 77 years). Fifty-five (95%) patients were active smokers. The most frequent symptoms were cough, chest pain, and dyspnea. SCLC was staged as extensive disease in 40 patients (66.7%) and limited disease in 20 cases (33.3%). For diffuse stages, chemotherapy was possible in 34 (85 %) of patients. We observed 2 (5%) complete responses, 9 (22.5%) partial responses, 3 (7.5%) stable diseases, and 9 (22.5%) progressions. Only 11 patients (27.5%) received second line chemotherapy with a median time to progression of 2.2 months. Five patients died, 1 had partial response, and 3 had progressive disease. One patient received third line chemotherapy. For localized stages, 7 (35%) patients received concomitant radiochemotherapy, 5 (25%) primary chemotherapy followed by concomitant radiochemotherapy, and 8 (40%) sequential treatment. Two (10%) patients had complete response, 8 (40%) partial response, 3 (15%) stable disease, 4 (20%) progressive disease, and 1 patient died. Twelve patients relapsed (60%) with a median time to progression of 2 months. Ten patients received relapse chemotherapy. Four patients died from their disease and 4 had a progressive disease. The median survival was 10 months for the overall population, 12.5 months, and 9 months for localized stages and diffuse stages, respectively.
Conclusions: In diffuse SCLC and even with ECOG performance status 0 to 2, first line chemotherapy was feasible in only 85% of cases and second line in only 27.5%. In localized disease, upfront therapy and relapse therapy were possible for 100% and 83% of cases, respectively.

Keywords: Small Cell Lung Cancer, Performance Status, Stage, Therapy

1. Background

Lung cancer leads cancer-related mortality worldwide. Small cell lung cancer (SCLC) is the most aggressive type, currently accounting for 14% of all lung cancers, or approximately 30,000 patients annually in the US (1). In Tunisia, it represents 11.8% of all lung cancers (2). Tobacco exposure is strongly associated with the development of SCLC, with only 2% to 3% of patients being never-smokers (3).

It is a neuroendocrine carcinoma of high grade and aggressive features. Its typical presentation is large hilar and/or mediastinal adenopathy and distant metastases. SCLC has traditionally been staged, using the veterans' affairs lung study group staging system, which subdivides tumors into limited-stage (LS) and extensive-stage (ES) based on the presence of tumor confinement into one hemithorax and included one radiotherapy port (4). TNM staging has a prognostic value, but it does not influence treatment decision. SCLC is characterized by a good sensitivity to chemotherapy and radiation therapy, and the majority of patients respond to upfront chemotherapy or concurrent chemoradiation. However, the rapid deterioration of general health condition in the majority of patients makes therapy non-feasible. Most patients develop recurrence and prognosis of such patient's poor (5).

The aim of this study was to describe the clinical characteristics and therapeutic results of good performance status of SCLC in Tunisian patients.

2. Methods

We retrospectively analyzed 60 patients diagnosed with SCLC in our department over a period of 5 years (2011 - 2015). Only patients with eastern cooperative oncology group (ECOG) performance status 0 to 2 were included in this study. The data including clinical and radiological findings and treatment modalities, response, and survival were collected based on the patients' records. Work-up included computed tomography (CT) and bone scan. Staging was based on veterans' affairs lung study group staging system: Limited disease is defined by tumors confined to one hemithorax, and/or to ipsilateral and/or same side supraclavicular nodes, which could be encompassed in the same radiation portal. All other cases were classified as extensive disease. Statistical evaluation statistical analyses were performed with SPSS (statistical package for social sciences) software.

The study was approved by the local ethical committee of the hospital; the study was conducted according to the World Medical Association's Declaration of Helsinki. Considering the retrospective aspect of the study no written consent was needed.

Table 1. Population Characteristics

Characteristics	No. (%)
Patients (n)	60
Median age, y	61 ± 8.5
Sex	
Male	57 (95)
Female	3 (5)
Stage	
Limited stage (LS)	20 (33.3)
Extensive stage (ES)	40 (66.7)
Smoking	60 (100)
ECOG	
0	10 (16.7)
1	38 (63.3)
2	12 (20)
Stage	
IIB	3 (5)
IIIA	7 (11.7)
IIIB	5 (8.3)
IV	42 (70)
Unspecified	3 (5)

Abbreviation: ECOG, eastern cooperative oncology group.

3. Results

Sixty patients were enrolled during the study period. The mean age was 61.8 years (range 45 - 77 years) and sex-ratio was 19 (57/3). All patients were smokers: 57 patients (95%) were active smokers (median of 53 pack-years) and 3 patients were passive smokers. The most frequent presentation symptoms were cough (28%), chest pain (22%), dyspnea (13.6%), hemoptysis (10.2%), and weight loss (8.5%), respectively. The majority of cases (80%) had an ECOG good performance status (0 - 1).

Population characteristics were described in Table 1.

Most common metastatic sites were pleura (16.6%), bone (12%), and brain (12%). Liver, adrenal gland, and adrenal gland metastases were rare (2% - 4%).

For diffuse stages, the first line chemotherapy procedure was applied to 34 (85 %) patients (Etoposide-cisplatin: 24, Etoposide-Carboplatin: 5, Irinotecan: 2 and Irinotecan -cisplatin: 2). The patients received an average of 3.9 cycles of chemotherapy. Two (5%) patients had complete response, 9 patients (22.5%) partial response, 3 patients (7.5%) stable disease, 9 patients (22.5%) progressive disease, 7 patients (17.5%) lost of view, and 9 patients (22.5%) died from progression of the disease. Only 11 patients (27.5%) could receive second line chemotherapy with a median time to progression of 2.2 months (etoposide-cisplatin: 1, Irinotecan: 6 and Irenotecan -cisplatin: 3, gemcitabin: 1) with an average of 2.5 cycles. Five patients died, 1 had partial response, 3 had progressive disease, and 2 patients were lost follow-up. Two patients received third line chemotherapy with progression. For localized stages, 7 (35%) patients received concomitant radiochemotherapy, 5 (25%) primary chemotherapy followed by concomitant radiochemotherapy, and 8 (40%) sequential treatment with chemotherapy and, then, radiotherapy. All patients had etoposide-cisplatin as type of chemotherapy. Only 2 patients have not received thoracic radiotherapy (1 lost follow-up and the other progressed during first line chemotherapy). Two (10%) patients had complete response, 8 (40%) partial response, 3 (15%) stable disease, 4 (20%) progressive disease, 2 (10%) lost of view, and 1 patient died. Three patients had a prophylactic brain irradiation after the local control of the disease. Twelve patients relapsed (2 loco-regional relapse and 10 distant relapses) with a median time to progression of 2 months. Ten patients received second line chemotherapy (etoposide-cisplatin: 1, Irinotecan: 5, Irinotecan -cisplatin: 3, CAV Cyclophosphamide / Doxorubicin / Vincristine: 1). Four patients died from their disease, 4 had a progressive disease, 1 stable disease, and 1 partial response. Response to second line according to the time to relapse is shown in Table 2.

Two patients received third line chemotherapy and had progression. The mean survival rate was 12.5 months, 9 months, and 10 months for localized stages, diffuse stages,

Table 2. Response to Second Line According to the Time to Relapse

	Time to Progression, mo	Type of 2nd Line Chemotherapy	Response
Patient 1	1	Irenotecan -cisplatin	Progression
Patient 2	1	Irenotecan	Stable disease
Patient 3	5	Irenotecan	Death
Patient 4	5	Irenotecan -cisplatin	Death
Patient 5	2	Irenotecan -cisplatin	Partial response
Patient 6	4	Irenotecan	Progression
Patient 7	2	CAV	Progression
Patient 8	14	Etoposide-cisplatin	Death
Patient 9	1	Irenotecan	Progression
Patient 10	2	Irenotecan	Death

Abbreviation: CAV, Cyclophosphamide/Doxorubicin/Vincristine

and overall patients, respectively. One patient survived longer than 5 years (72 months). This case was a 70-year-old female, who had been treated since 2010 for localized SCLC. She had a primary chemotherapy and, then, concomitant chemoradiotherapy. Two months later, she was presented with bone metastases. She had 6 cycles of cisplatin and Irinotecan with stable disease, thereafter.

For 3 patients, early palliative care was indicated, given the rapid alteration of the performance status, and they died in a median time of 1 month.

4. Discussion

We reported daily practice aspects of a patient population of SCLC with good performance status at presentation treated over 5 years in Tunisia.

The mean age was 61.88 $\pm$ 8.51 years, being in accordance with the literature (6). As reported by many studies, smoking is associated with SCLC; more than 98 % of the patients are previous smokers (7). We found that 57 (95%) patients were current smokers. Three other patients were passive smokers. There is no specific symptom of SCLC; patients generally have an association of signs related to local, regional, and/or distant spread. Weight loss and anorexia are very common (8).

Approximately, one third of patients in our study were diagnosed with limited-stage disease. It is a potentially 'curable' stage with definitive combined-modality therapy. Cisplatin-based chemotherapy is administered concurrently with thoracic radiotherapy, followed by prophylactic cranial radiation, which remains the standard practice for patients with good performance status (9). Although the use of hyperfractionated thoracic radiotherapy given in 2 fractions per day is considered the standard approach, its adoption has been challenged by practical and logistical realities for individual patients and care providers, especially in limited resources countries (9).

For extensive-stage SCLC, systemic chemotherapy generally allows high response rates, but the major problem remains a short duration and the small benefit (9). In fact, the majority of patients will show clinical or radiological sign of progression within 2 to 4 months (10). The general health condition and duration of response to chemotherapy are the most relevant factors to indicate further therapies. Several studies have reported the possible benefit of re-challenge with the similar drugs used in the initial therapy with a rational of possible sensitive relapse in long relapse free interval patients (10). In the JCOG0605 phase III trial, 180 patients with "sensitive" relapsed small-cell lung cancer were assigned to second-line therapy with single-agent topotecan or a weekly regimen of cisplatin, etoposide, and irinotecan. The results showed a significant improvement in overall survival with a combination therapy (median 18.2 months with combination therapy vs 12.5 months with topotecan; with a hazard ration of 0.67 [0.51 - 0.88], P = 0.0079). The combination of cisplatin, etoposide, and irinotecan could become the standard treatment for the selected patients with sensitive relapsed small-cell lung cancer (11). However, refractory relapse is chemo-resistant with responses seen in less than 10%, usually using monotherapy. Consequently, even though a large number of chemotherapy regimens were tested in clinical trials and some showed promising antitumor activities, topotecan was considered the second-line chemotherapy (12). In the present study, and given the unavailability of topotecan in our country, we use irenotecan as second-line chemotherapy.

The administration of chemotherapy concurrently with molecularly targeted agents, such as anti-angiogenic agents, hedgehog pathway inhibitors, and insulin like growth factor receptor inhibitors has failed to improve treatment outcomes (13). The emergence of immune checkpoint inhibitors for the treatment of cancer has provided new hope for patients. In SCLC, phase I and II studies have demonstrated encouraging response rates with monoclonal anti-bodies that target the programmed death-1 (PD-1) receptor (14). Furthermore, combination therapy with a PD-1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor yielded an objective response rate of approximately 30% in patients, who had progressed on prior platinum-based therapy. Larger phase II and III studies are being initiated to evaluate the roles of immune checkpoint inhibitors and novel combination strategies in

patients with SCLC (15).

Prognosis in SCLC is very poor. Without therapy reported, survival is around 2 to 4 months. The most important prognostic factors are disease extent and performance status.

4.1. Conclusions

Although patients with SCLC are highly responsive to chemotherapy and radiation therapy, long-term prognosis remains poor, with relapse and disease recurrence occurring in almost all cases. Continued research is necessary to better optimize patient selection and response to therapy.

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Footnotes

Authors' Contribution: Study concept and design: Houda El Benna, Azza Guebsi; acquisition of data: Azza Gubsi; analysis and interpretation of data: Azza Guebsi, Houda El Benna; drafting of the manuscript: Azza Gubsi, Houda El Benna, Nesrine Mejri; critical revision of the manuscript for important intellectual content: Hamouda Boussen; statistical analysis: Soumaya Labidi, Nouha Daoud; administrative, technical, and material support: Afrit Mahdi; study supervision: Hamouda Boussen.

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