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Original Article

Survival and Prognostic Factors in Small Cell Lung Cancer Patients in Turkey

F. Ece, N. Erdal, S. Arinc

Abstract

Background: Small cell lung cancer (SCLC) is a highly aggressive tumor.

Objective: To evaluate the survival and time to progression of patients with SCLC admitted to a chest disease center in Istanbul, Turkey.

Methods: Based on the reports of a pulmonary oncology clinic, data regarding performance status (PS), clinical stage of disease, treatment, time to progression and survival of 67 patients with SCLC diagnosed between 1999 and 2002, were examined.

Results: The median survival time of these patients was 10 months (range: 4-21 months). The median time to progression was 7.2 months; 7.2 months for limited stage and 7.1 for extended stage. Complete and partial responses with first line chemotherapy were achieved in 19 (28%) and 29 (43%) patients, respectively. 30 patients (45%) received thorax radiotherapy (RT). Survival in patients who had thoracic RT was significantly longer than others (p=0.018). 26 of all patients (39%) showed progression within 6 months after first line chemotherapy. 19 patients (28%) received second line chemotherapy with complete response achieved in 2 patients.

Conclusion: Main factors affecting survival and length of time to progression were PS, stage of disease, and cigarette smoking. Patients with good PS, limited disease, and less smoking had superior survival times and longer time to progression.

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Keywords • Small cell lung cancer • survival • prognostic factors

Introduction

Small cell lung cancer (SCLC) displays a highly aggressive clinical behavior. Untreated patients rarely survive beyond a few months, and local treatment modalities like radiation therapy (RT) or surgery are not effective in increasing survival beyond a few weeks.[1,2] SCLC, however, is markedly chemosensitive in most patients on diagnosis and the in-charge physicians are often pleased to observe dramatic shrinkages in large tumor masses. The oncologist, nevertheless, is too often frustrated when they discover that within a few months, tumor progression has occurred.[3] Although

Pulmonary Oncology Clinic, SSK Sureyyapasa Chest and Cardiovascular Diseases Hospital, Istanbul, Turkey

Correspondence: F. Ece, MD
Atakoy 11. Kisim Menekse, D Girisi D:37 34750 Istanbul, Turkey
Tel: +90-212-560-8319
Fax: +90-216-370-6996
E-mail: fkorap@hotmail.com

Table 1: Patient characteristics

Age	**n (%)**
<60	37 (55.2)
≥60	30 (44.8)
Sex	
Female	12 (17.9)
Male	55 (82.1)
ECOG PS	
0	31 (46.3)
1	26 (38.8)
2	9 (13.4)
3	1 (1.5)
Smoking	
<50 pack/year	40 (59.7)
≥50 pack/year	27 (40.3)
Thorax RT	
No	35(53.8)
Yes	30 (46.2)

Table 2: Disease characteristics

Stage	**n (%)**
Limited	46 (68.7)
Extensive	21 (31.3)
Tumor localization	
Right upper lobe	19 (28.4)
Right middle lobe	7 (10.4)
Right lower lobe	4 (6.0)
Left upper lobe-lingula	23 (34.3)
Left lower lobe	6 (9.0)
Hilar (R or L)	8 (11.9)
Pleural effusion	
No	57 (85.1)
Yes	10 (14.9)
Tumor diameter (cm)	
<3	6 (9.0)
≥3	61 (91.0)

survival is significantly improved with chemotherapy, most patients succumb to their disease within one year of diagnosis. Combination chemo therapy is the cornerstone of treatment for these patients, yielding high initial response rates of 65% to 85%, including 10% to 50% complete responses, depending on disease stage.[4,5] The optimal induction regimens are either EP or CAV-based.[6] Meta-analysis of chemotherapy regimens with or without cisplatin demonstrated a significant increase in response rate and survival with no significant increase in toxicity when cisplatin is added.[7] RT is generally accepted as an essential component of optimal management of the limited-stage disease.[8] For limited disease, the addition of thoracic RT for all patients and prophylactic cranial irradiation (PCI) in complete or near complete responders have improved survival.[9] Earlier concurrent therapy and rather brief intense chemotherapy and RT seem to produce the best results in moderately fit patients of all ages.[10] On relapse, some patients may still be in good physical condition and thus, deserve further treatment.

The aim of this study is to evaluate the survival and time to progression of patients with SCLC and report the results of a chest disease center in Istanbul, Turkey.

Patients and Methods

We retrospectively, reviewed and analyzed records of patients with cytopathologic diagnosis of SCLC in Istanbul SSK Sureyyapasa Hospital Pulmonary Oncology Clinic from 1999 to 2002.

Limited disease group included patients with lesions confined to ipsilateral hemithorax, regional and supra-clavicular lymph nodes. Extensive disease was characterized by an evident and/or proven metastasis. A complete blood count (CBC), urinalysis, serum biochemistry profile, ECG, chest roentgenography, brain and chest computerized tomography (CT) scans were performed prior to chemotherapy. The patients' clinical characteristics including their performance status (PS), age, smoking history, stage of disease, presence of pleural effusion, treatment modalities, time to progression, and any treatment-associated toxicities were also recorded. The patients who relapsed or progressed received second line chemotherapy. The family of patients who had been lost to follow-up was contacted to establish the approximate date of death. The overall survival and time to progression were defined as the time from diagnosis to the date of death.

Patients received 75 mg/m^2 cisplatin on day 1 and 100 mg/m^2 etoposide on day 1, 2, and 3 every 3 weeks, as the first line chemotherapy. The second line therapy consisted of 1000 mg/m^2 cyclophosphamide, 50 mg/m^2 epirubicin, and 2 mg vincristine, all administered on day 1 every 3 weeks. All infusions were given through a central venous line. Dexamethasone and ondansetron were given before chemotherapy as antiemetic prophylaxis. For dose adjustments in the subsequent cycle, a 50% reduction in chemotherapeutics was instituted when the patient suffered from grade 4 neutropenia or thrombocytopenia. A CBC was repeated before every injection. A serum biochemistry test was performed before and during every course of chemotherapy, if clinically indicated. Chest roentgenography was performed before every course of chemotherapy. In case of any symptomatic sufferings, according to the estimated localization of the metastatic lesion, MRI was performed and palliative RT or another symptomatic treatment was instituted immediately. Responses and drug-related toxicities were evaluated according to the WHO criteria.

Table 3: Localization of developed metastasis in patients with limited stage SCLC

Site of Metastasis	n (%)
Brain	12 (44.4)
Liver	5 (18.5)
Bone	2 (7.4)
Suprarenal gland	1 (3.7)
Multiple	4 (14.8)
Contralateral lung	3 (11.1)

A complete response (CR) was defined as the disappearance of all malignant lesions documented by clinical and radiological methods lasting for a minimum of one month. A partial response (PR) was defined as a decrease of >50% in the size of all measurable lesions lasting for one month without any new tumor lesion. Stable disease (SD) was defined as a decrease of <50% or an increase of <25% in the cross-sectional area of one or more lesions. Progressive disease (PD) was defined as an increase of at least >25% in the cross-sectional area of one or more lesions. In responding patients and in patients with stable disease, a maximum of six cycles of chemotherapy was given in the first line. Eligible patients with limited stage SCLC were given concurrent thoracic radiotherapy (TRT) after the first line chemotherapy. Patients with pleural effusions and obstructive lung disease (FEV_1 <30% predicted value) did not receive RT, despite their limited SCLC. Age, history of smoking, diameter of primary tumor, presence of pleural effusion, PS, response to initial chemotherapy, response after combined chemotherapy plus RT, serum LDH levels before chemotherapy, were all determined for prognostication.

Statistical methods

SPSS was used for statistical analyses. Mann Whitney-U and Kruskal Wallis tests were used to evaluate prognostic factors for the longer survival. The Kaplan-Meier survival analysis method was used for estimating time-to-event measures.

Results

Sixty-seven patients—46 with limited and 21 with extensive stage disease—were enrolled into the study. The diagnosis of SCLC was made by fiberoptic bronchoscopy in 56 patients (84%), peripheral lymph node biopsy in 6 (9%), mediastinoscopy in 1 (1%), and other methods (*eg*, TTNA, liver biopsy, *etc.*) in 4 (6%) patients. Patient and disease characteristics are shown in Tables 1 and 2, respectively. All patients were ex-smoker. The majority of patients were male with good PS. A pretreatment LDH level was high in 20 (30%) patients. Twenty seven (40%) of 46 patients with limited SCLC developed distant metastasis most commonly to the brain (Table 3) after a median period of 7.6 (range: 2–15) months.

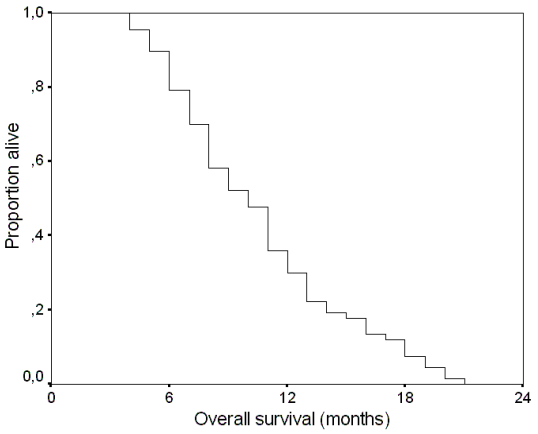

Fig 1: Survival curve of the patients

A total of 352 chemotherapy cycles were given to all patients as the first line chemotherapy. The median number of treatment cycles was 5 (range: 2–6) cycles/patient. Dose reduction was necessary in 9 patients, due to development of grade 4 neutropenia in 8 and grade 4 trombocytopenia in one patient. Febrile neutropenia occurred in one of them (13%). There were several other non-hematologic toxicities such as nausea, vomiting, fatigue, loss of appetite, and alopecia. Chemotherapy response rates are shown in Table 4. Thirty patients (46%) received TRT after first line chemotherapy. Twenty three patients (36%) received palliative RT because of distant metastasis (14 to the brain, 6 to bone, and 3 to other sites).

Nineteen patients (28%) received second line chemotherapy. A total of 56 cycles of second line chemotherapy were given to 19 patients. No toxicity was observed after the second line therapy. Responses included CR in 2 patients (11%), PR in 3 (16%), SD in 8 (42%) and PD in 6 patients (32%).

The median survival time of patients was 10 (range: 4–21) months (Fig 1). Five patients (8%) lived longer than 18 months. The median time to progression was 7.2 (range: 3–18) months with 72 in limited and 7.1 in extensive stages. The median survival time of patients according to their response after first line chemotherapy is shown in Table 5.

Twenty six patients (39%) showed progression within 6 months after first line chemotherapy. There was no significant difference between survival time and time to progression when comparison was made between age groups (≥60 and <60 years), localization of lesions, presence of pleural effusion, tumor diameter, and serum LDH levels. Patients with

Table 4: Response rates after first line chemotherapy

Response	n (%)
Complete response	19 (28.4)
Partial response	29 (43.3)
Stable disease	17 (25.4)
Progressive disease	2 (3.0)

Table 5: Survival of patients according to response rates after first line chemotherapy

Response	Survival (month)
Complete response	11 (6-13)
Partial response	8 (4-19)
Stable disease	8 (4-16)
Progressive disease	5 (4-6)

good PS (0-1) (p=0.038), limited disease (p=0.39), and less smoking (<50 pack/year) (p=0.29) lived longer than others and had longer time to progression (p values of 0.002, 0.047 and 0.021, respectively). Survival time was also significantly longer in patients receiving TRT (p=0.018).

Discussion

This study was designed to determine the incidence of progression, prognostic factors and survival of patients with SCLC in a chest disease center in Istanbul, Turkey. The major outcome variables, survival time and time to progression were measured from the time of diagnosis to death, and progression, respectively. Our results demonstrated that PS, limited stage disease, and history of smoking were the variables that achieved statistical significance among 8 predictors assessed (LDH level, PS, history of smoking, age, tumor diameter, stage, presence of pleural effusion and localization of lesions).

Our finding of good PS and limited disease associating with long survival is in accord with those of several investigations.[11-15] Recently published studies emphasized the importance of stage in predicting the response to treatment and survival.[14,16] Our findings were similar to that of southwestern oncology group with respect to PS as an important favorable factor in limited stage SCLC.[17] However, our findings, differing from this study and those of Tai *et al.*, demonstrated that young patients lived significantly longer.[18] We found no correlation between age and survival. It has been reported that increased LDH levels were associated with significantly shorter survival.[11,12,15,19-21] In our study, though was not statistically significant, patients with elevated serum LDH levels had a shorter survival and time to progression which is in keeping with those studies. Because of most of our patients were men, we could not compare sex differences. Nonetheless, there are some studies revealing a longer survival in female patients.[13,22,23] Complete response after second treatment with initial chemotherapy has been reported, however, in our study, we achieved CR in only 2 patients with a different regimen.[24] TRT affects the results of patients with limited stage disease. There is a general agreement that patients with limited SCLC are better treated with a combination of TRT and systemic chemotherapy than with either modality alone.[25] We also found that survival was significantly longer in patients who received TRT.

There are some limitations to our study. The relatively small number of patients does not allow for meaningful conclusion about prognostic factors. In addition because our patient population was mostly men, we could not comment on the effect of gender for time to progression and length of survival.

In conclusion, we can emphasize that SCLC patients with good PS, limited disease, and less smoking had statistically superior survival times and longer time to progression.

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