RESEARCH COMMUNICATION

Is Diabetes Mellitus a Prognostic Factor for Survival in Patients with Small Cell Lung Cancer?

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Abstract

Background: Previous studies have pointed to many different prognostic factors for small cell lung cancer (SCLC) but diabetes mellitus (DM) has not been clearly or consistently identified as of prognostic value. The aim of this study was to investigate the prognostic significance of the characteristics of patients and clinical laboratory tests in SCLC. Specifically, we investigated that the impact of DM for survival in the patients receiving first-line etoposide plus cisplatin (EP) chemotherapy. Methods: We retrospectively reviewed 161 patients with SCLC with a focus on DM and other potential prognostic variables were chosen for univariate and multivariate analyses with respect to survival. Result: Among the sixteen variables of univariate analysis, five were identified to have prognostic significance: performance status (PS) (p <0.001), stage (p=0.001), DM (p=0.005), serum albumin (p <0.001) and hemoglobin levels (p=0.03). Multivariate analysis showed PS, stage and serum albumin level to be independent prognostic factors for survival (p=0.02, p=0.02 and p=0.009 respectively), but DM was not an independnet factor. Conclusion: In conclusion, PS, stage and serum albumin level were identified as important prognostic factors, while DM at the time of diagnosis of SCLC did not have prognostic importance for survival.

Keywords: Small cell lung cancer - prognostic factors - diabetes mellitus - serum factors

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Introduction

Lung cancer is the most common among cause of cancer deaths in both men and women in worldwide. SCLC represent approximately 15% of all the diagnosed lung cancers cases (Boyle et al., 2004; Serke et al., 2007). SCLC is very sensitive to radiotherapy and chemotherapy while it is associated with a more rapid tumor doubling time, a high growth fraction and early widespread dissemination. As a result of this, the overall 5-year survival rate among SCLC patients are stil less than 10% (Zelen et al., 1973; Lassen et al., 1995).

Systemic chemotherapy with the combination of etoposide plus cisplatin (EP) is currently recommended as a standard of first-line chemotherapy for treatment of SCLC (Jackman et al., 2005). Although the median survival for limited disease (LD) is 14 to 16 months and only 8 to 11 months for extensive disease (ED) with the effective treatment, without effective treatment, the median survival for SCLC is only 2 to 4 months (Boyle et al., 2005; Pelayo et al., 2009).

The Veterans Administration Lung Study Group two-tiered staging system was used to classify SCLC as either ED or LD that was principally based on suitably for treatment options (Fry et al., 1996). Though its practical usefulness, this classification system is not satisfactory to reflect tumor burden and it is insufficient to predict survival in a part of the patients.

A number of very different prognostic factors in several trials have been identified for survival in patients with SCLCs (Cerny et al., 1987; Albain et al., 1990; Yip et al., 2000; Tas et al., 2001; Sculier et al., 2008; Foster et al., 2009). It was demonstrated previously parameters that good PS, disease stage, age and weight loss associated as strong prognostic factors whereas DM was not clearly or consistently identified (Park et al., 2006; Van de Poll et al., 2007; Barone et al., 2008; Win et al., 2008; Varlotto et al., 2011).

The aim of this study was to investigate the prognostic significance of the characteristics of patients and results of clinical laboratory tests in SCLC. Specifically, we investigated the impact of diabetes mellitus for survival in patients receiving first-line EP chemotherapy.

Materials and Methods

Patient Population

We retrospectively reviewed 161 patients with histologically or cytologically proven SCLC who patients receiving first-line EP chemotherapy from June 2001

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Table 1. The General Characteristics of the Patients

Characteristic		No. of patients
Sex:	Male	146
	Female	15
Age, median (range)		57 (28-81)
Age:	<65	127
	≥65	34
Performance status:	0-1	87
	2-3	62
	Unknown	12
Smoking history:		
	Current or former	120
	Never	14
	Unknown	27
Weight loss:	Yes	37
	No	100
	Unknown	24
Hemoptysis:	Yes	31
	No	109
	Unknown	21
Diabetes Mellitus:	Yes	21
	No	117
	Unknown	23
Stage:	LD	78
	ED	83
Laboratory parameters, median:		
	Hemoglobin, g/l	12.9
	WBC	8730
	Albumin, g/dl	3.3
	ALT, U/l	20
	LDH, U/l	322
	Calcium, mg/dl	9.4
	Creatinine, mg/dL	0.8
	Blood sugar, mg/dl	106

to December 2011 in the Dicle University, School of Medicine, Department of Medical Oncology.

Factors Analyzed

Sixteen potential prognostic variables were chosen on the basis of previously published clinical trials. The variables were divided to categories: age (<65 or ≥ 65), gender (male or female), PS (0-1, 2-3), stage (LD or ED), weight loss ≥ 5% with previous 3 months (present or absent), DM (present or absent), smoking history (present or absent), hemoptysis (present or absent) and laboratory parameters (< median or ≥ median) at the time of first-line chemotherapy administration.

Statistical Analysis

All of the analyses were performed using the SPSS statistical software program package (SPSS version 11.5 for windows). The differences of the clinical characteristics between the two groups were analyzed by chi-square test and student t test. OS was calculated from the start of the first cycle of chemotherapy to the date of death from any cause or the date of the last follow-up. OS was estimated using the Kaplan-Meier method. The Cox proportional hazards regression model was used to determine statistical significant variables related to survival. Differences were assumed to be significant when P value of less than 0.05.

Results

Table 2. Univariate Analysis of Survival Time by Categorical Variable

Variable	Log-rank test value	Degrees of freedom	p
Sex	0.01	1	0.91
Age	1.29	1	0.25
Stage	10.22	1	0.001
Smoking history	0.97	1	0.32
Performance status	19.7	1	<0.001
Weight loss	1.18	1	0.27
Hemoptysis	0.34	1	0.55
Diabetes Mellitus	7.81	1	0.005
Laboratory parameters, median			
Hemoglobin	4.63	1	0.03
WBC	0.002	1	0.96
Albumin	12.7	1	<0.001
ALT	1.39	1	0.23
LDH	0.95	1	0.32
Calcium	1.92	1	0.16
Creatinine	0.78	1	0.37
Blood sugar	1.30	1	0.25

Table 3. Multivariate Analysis of Prognostic Factors

Parameter	OR	%95 CI	p value
Performance status	2.17	1.10-4.25	0.02
Stage	2.15	1.10-4.22	0.02
Albumin	0.42	0.22-0.80	0.009

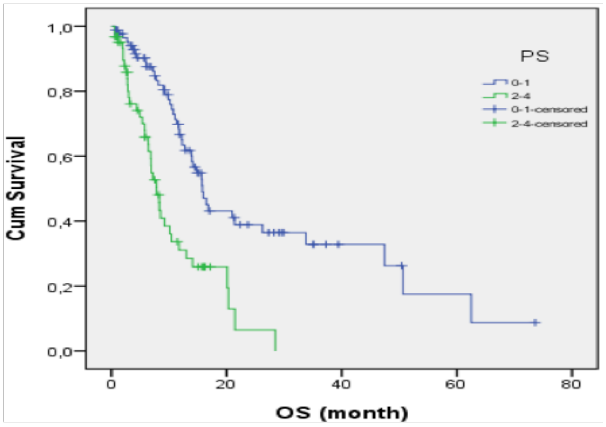

Figure 1. Survival of Patients According to Performance Status

Patient Characteristics

Between June 2001 to December 2011, 161 patients with SCLC were enrolled in this study. The median age of patients was 57 years (range 28–81) with 146 (90.7%) males and 15 (9.3%) females. The number of patients with a PS score 0–1 was 87 (54.0%). Eighty-three patients (51.6%) were diagnosed as having ED and 78 patients (48.4%) had LD. The estimated median OS with LD was 15.9 months (95% CI, 6.8–24.9 months). Median OS of the treated ED patients was 9.9 months (95% CI, 7.5–12.4 months). The patients' baseline characteristics are listed in Table 1.

Prognostic Factor Analysis

The results of univariate analysis are summarized in Table 2. Among the sixteen variables of univariate analysis, five variables were identified to have prognostic significance: PS ($p < 0.001$), stage ($p=0.001$), DM

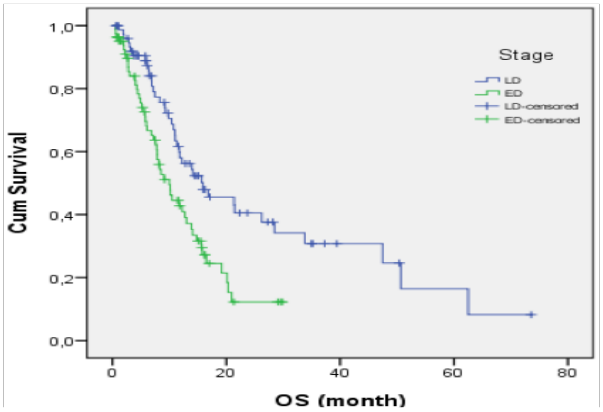

Figure 2. Survival of Patients According to Stage

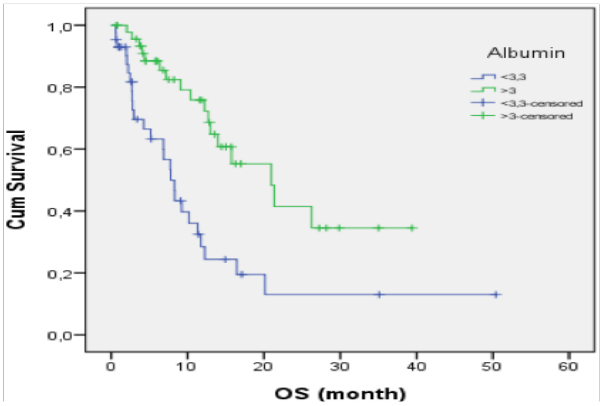

Figure 3. Survival of Patients According to Serum Albumin Level

(p=0.005), serum albumin (p < 0.001) and hemoglobin levels (p=0.03).

Multivariate analysis included the five prognostic significance factors in univariate analysis. The results are shown in Table 3. Multivariate analysis by Cox proportional hazard model showed that PS, stage and serum albumin level were considered independent prognostic factors for survival (p=0.02, p=0.02 and p=0.009 respectively) (Figure 1, 2, 3).

Discussion

SCLC is very sensitive to radiotherapy and chemotherapy while it is associated with a more rapid tumor doubling time, a high growth fraction and early widespread dissemination. As a result of this, the overall 5-year survival rate among SCLC patients are still less than 10% (Zelen et al., 1973; Lassen et al., 1995). Patients eligible for chemotherapy should be selected attentively. A very different prognostic factors in several trials have been identified for survival in patients with SCLC (Cerny et al., 1987; Albain et al., 1990; Yip et al., 2000; Tas et al., 2001; Sculier et al., 2008; Foster et al., 2009), however none of this prognostic factors are reliable adequate to base treatment decision on. This retrospective study analyzed prognostic factors for OS in SCLC patients who were undergoing first-line chemotherapy with EP.

On univariate analysis, Among the sixteen variables of univariate analysis, five variables were identified to have prognostic significance: PS (p < 0.001), stage (p=0.001), DM (p=0.005), serum albumin (p < 0.001) and hemoglobin levels (p=0.03). However, only 3 independent significant prognostic factors were found on multivariate analysis: PS, stage and serum albumin level were considered independent prognostic factors for survival (p=0.02, p=0.02 and p=0.009 respectively).

Numerous studies have reported a strong independent prognostic importance of PS in all cancer patients (Tammemagi et al., 2003; Mitry et al., 2004; Krishnan et al., 2006). The significance of PS was also confirmed in SCLC patients (Foster et al., 2009). Like other authors, we found that poor PS is associated independent risk factor for survival.

The median survival for LD is 14 to 16 months and only 8 to 11 months for ED with the effective treatment. The overall 5-year survival rate is under 10% (Boyle et al., 2005; Pelayo et al., 2009). The previously by a number of authors (Lassen et al., 1995; Bremnes et al., 2003; Sculier et al., 2008; Hansen et al., 2010) had showed that the tumor stage at initial presentation was the most important prognostic factor for survival in patients with SCLC. Similarly stage of disease was found to be an independent prognostic factor of survival in the present retrospective study. In our study, the estimated median OS for LD was 15.9 months (95% CI, 6.8–24.9 months) and only 9.9 months (95% CI, 7.1–9.8 months) for ED.

An association between decreased serum albumin level and decreased survival has been demonstrated in patients with SCLC (Quoix et al., 2000; Hansen et al., 2010). Similarly serum level of albumin was found to be an independent prognostic factor of survival in our study. The decreased serum albumin level may play a role in the pathogenesis of cancer cachexia. The serum albumin level may indicate the patient's nutritional status. The consequences of malnutrition may include increased risk of complications, reduced performance status, decreased response and tolerance to chemotherapy.

A very different epidemiological trials have linked pre-existing DM at the time of diagnosis with an increased mortality rate for breast cancer patients cancer and colorectal patients (Huang et al., 2011; Peairs et al., 2011). However, there are a few studies about the impact of diabetes mellitus for survival in SCLC. It is limited and conflicting. Although the few prior studies (Park et al., 2006; Van de Poll et al., 2007; Win et al., 2008; Varlotto et al., 2011) showed that pre-existing DM that at the time of diagnosis strongly associated increase OS. Contrary to this, the meta-analysis analysis by Barone et al. (2008) and the study of Tammemagi et al. (2003) no observed this relationship between diabetes and lung cancer. In our retrospective study, we found that the DM no associated with the prognostic importance for survival.

The present study has got some limitations. First, its retrospective study. Second, we did not evaluate the type of DM, duration of diabetes and the types of diabetic therapy used. Third, our findings have biased a selection because of possibilities of undiagnosed DM among patients classified as not having DM.

In conclusion, performance status, stage and serum albumin level were identified as important prognostic factors, while DM at the time of diagnosis no associated with the prognostic importance for survival in patients

with SCLC. It may be concluded that these findings may also facilitate pretreatment prediction of survival and can be used for selecting patients for the correct choice of treatment.

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