RESEARCH ARTICLE

Prognostic Factors for Survival of Patients with Extensive Stage Small Cell Lung Cancer - a Retrospective Single Institution Analysis

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Abstract

The objective of this retrospective study was to investigate prognostic factors associated with survival of patients with extensive stage small cell lung cancer (ES-SCLC). Included were 200 patients admitted to the Liberation Army General Hospital with a diagnosis of ES-SCLC. The demographics of patients, disease characteristics, pre-treatment biochemical parameters and therapeutic plan were assessed or evaluated. Univariate analysis found that second-line chemotherapy, radiotherapy, and no liver metastasis were associated with improved survival. Tumor response to first-line chemotherapy and normal initial hemoglobin levels were also associated with a survival benefit (all P-values ≤ 0.0369). Multivariate Cox regression analysis indicated that liver metastasis and the total number of all chemotherapy cycles were independent prognostic factors of survival. The morbidity risk in patients with liver metastasis was 2.52-fold higher than that in patients without liver metastasis (hazard ratio (HR)=2.52 (1.69-3.76); P<0.0001). However, one unit increase in the total number of chemotherapy cycles decreased the risk of death by 0.86-fold (HR=0.86 (0.80-0.92); P<0.0001). Absence of liver metastasis and ability of a patient to receive and tolerate multiple lines of chemotherapy were associated with longer survival.

Keywords: Small cell lung cancer - extensive stage - prognosis - liver metastasis - chemotherapy

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Introduction

Lung cancer is the most commonly diagnosed cancer world-wide and the leading cause of cancer death in males and the second cause of cancer death in females worldwide (Jemal et al., 2011). Small cell lung cancer (SCLC) accounts for approximately 15% to 18% of all lung cancers and is highly-associated with smoking (Khuder, 2001; Govindan et al., 2006). According to Neal et al, the Veterans Administration Lung Study Group staging system divides SCLC into limited stage (LS) and extensive stage (ES) disease (Neal et al., 2011). LS-SCLC involves primary tumor contained within one hemithorax and/or mediastinal nodes with ipsilateral supraclavicular disease. ES-SCLC refers to disease located beyond the LS areas that cannot be confined to a single radiotherapy portal and includes widely-metastatic disease.

Despite the high response rate to initial chemotherapy, the overall survival (OS) rate is low, with only 2% to 10% of patients with either LS-SCLC or ES-SCLC being alive at 5 years (Chua et al., 2004). The median survival time for patients with ES-SCLC is 12 months to 20 months depending on disease stage (Chua et al., 2004).

The low OS rate and the high relapse following first-line chemotherapy evident with SCLC warrant the identification of prognostic factors that may influence survival and treatment outcomes. Earlier studies have identified a number of factors that potentially may affect treatment response and long-term survival; however, the findings have not been consistent (Paesmans et al., 2000; Bremnes et al., 2003; Ando et al., 2004; Ustuner et al., 2008; Ou et al., 2009; Li et al., 2010). But the consistent conclusion was that the identification of prognostic factors might be useful for the better evaluation of treatment outcome in clinical trials and the use of a targeted and specific treatment of SCLC. Major goals for the treatment of ES-SCLC include prolonging survival, relieving symptoms, and improving patients' quality of life. The current standard treatment for ES-SCLC is chemotherapy and, when appropriate, local radiation therapy. Identifying factors that may help predict long-term survival may help healthcare professionals and patients make treatment decisions for managing the disease. In this retrospective study, we investigated prognostic factors for survival of Chinese patients with ES-SCLC.

Materials and Methods

Patients

We retrospectively reviewed and analyzed clinical

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records and pathology data of patients admitted to the Liberation Army General Hospital who were diagnosed with ES-SCLC from January 2005 to January 2010.

Eligible patients had ES-SCLC as defined by the United States Veterans Hospital. The diagnostic criteria included inoperable patients (no LS disease) with lesions involving the ipsilateral chest, malignant pleural effusion or pericardial effusion, distant metastasis, significant compression of the superior vena cava, and/or vocal cord paralysis (Micke et al., 2002). For all patients, baseline medical examinations included a bone scan, lung computed tomography (CT), brain magnetic resonance imaging (MRI), cervical lymph node examination, abdominal ultrasound, and adrenal ultrasound or CT.

All patients received first-line chemotherapy and a subset also received radiotherapy. Radiotherapy was predominately used as palliative care for patients with chest lesions, mediastinal and supraclavicular lymph nodes, or whole-brain or bone metastases. Chemotherapy included etoposide plus cisplatin or carboplatin, irinotecan plus cisplatin, or epirubicin (or doxorubicin) plus etoposide and cisplatin (or nedaplatin). Teniposide could replace etoposide.

Study design and measures

Tumor response to treatment was categorized as complete response, partial response, stable disease, and progressive disease based on Response Evaluation Criteria In Solid Tumors Guideline (Eisenhauer et al., 2009). During chemotherapy, patients were examined every 2 cycles to assess tumor response. Response rate was calculated as the proportion of patients who had complete or partial response.

For determining survival time, patients were followed by telephone from October 2010 until December 2010, and survival was calculated from the first day of diagnosis to last follow-up date.

This study included the following clinical prognostic indicators: age, gender, smoking history, presence of liver metastases, the number of cycles of first-line and total chemotherapy (including second- and third-line), whether the patient received second-line therapy or radiotherapy, and tumor response to first-line chemotherapy. Other parameters evaluated were initial levels of hemoglobin, lactate dehydrogenase (LDH), platelets, albumin, neuron-specific enolase (NSE), carcinoembryonic antigen (CEA), and CYFRA21-1. Whether a patient did or did not develop chemotherapy-related leukopenia was also assessed.

Statistical analysis

The survival of the patients by each characteristic was compared using log-rank statistics. Simple and multivariate Cox regression models were used to identify the risk factors. A P-value of 0.05 or less (in a two-sided test) was considered statistically significant. All analyses were performed using SPSS software, version 16.0 (SPSS, Chicago, IL).

Results

Of the 200 patients (174 male/26 female) eligible for this study, 95 patients were older than 60 years and 105 patients were younger than 60 years (Table 1). The majority of patients were smokers (77.5%) and had normal levels of hemoglobin, platelets, albumin, LDH, NSE, CEA, and CYFRA21-1. The majority of patients did not have liver metastasis (70%) and had experienced Grade 1 or 2 leukopenia (65%). Approximately half of the patients received second-line chemotherapy (42.5%) or radiotherapy (54.5%), in which 52 patients received both second-line chemotherapy and radiotherapy. The most common form of first-line chemotherapy was the combination of etoposide plus cisplatin (80%). Grade 3 or 4 leukopenia occurred in 39 (19.5%) patients.

Univariate analysis found that a higher survival rate and longer survival times were associated with patients who did not have liver metastasis or who were receiving

Table 1. Univariate Analysis of SCLC Patients with Extensive Stage

Variables	n	Survival rate, %			Median Survival Time, months (95% CI)	P-value
		12th month	24th month	36th month		
All	200	60.46	21.42	14.18	16 (13-17)	
Age						
>60	95	54.86	20.07	12.04	14 (12-17)	0.1768
<60	105	66.06	22.96	17.22	17 (13-18)	
Gender						
Male	174	62.35	22.35	15.28	16 (13-17)	0.4129
Female	26	48.82	16.27	0	12 (8-20)	
Smoker						
Yes	155	61.23	23.12	15.4	15 (13-17)	0.6498
No	45	57.8	15.66	10.44	16 (11-18)	
Hemoglobin						
Normal	142	70.99	28.56	17.31	17 (15-20)	0.0173
Low	23	40.19	13.4	13.4	10 (7-16)	
Platelets						
Normal	129	64.67	25.34	15.64	17 (14-19)	0.7705
High	37	68.27	26.23	19.67	17 (12-23)	
Albumin						
Normal	149	66.95	26.76	17.03	17 (15-18)	0.083
Low	21	57.03	10.86	0	13 (9-17)	
LDH						
Normal	118	70.35	23.18	13.52	17 (15-18)	0.6425
High	51	55.15	27.28	22.73	13 (11-20)	
NSE						
Normal	41	72.15	29.57	19.71	18 (16-24)	0.1725
High	124	64.11	22.51	14	16 (13-17)	
CEA						
Normal	97	72.43	21.88	16.67	17 (16-20)	0.5109
High	68	58.27	29.35	13.04	15 (12-19)	
CYFRA21-1						
Normal	108	72.1	32.63	19.13	17 (14-22)	0.067
High	53	54.69	11.26	11.26	15 (11-18)	
Liver metastasis						
Yes	56	32.66	9.16	9.16	11 (8-12)	<0.0001
No	140	73.98	27.18	16.81	17 (16-20)	
Second-line chemotherapy						
Yes	85	69	26.48	17.16	18 (13-21)	0.0369
No	105	55.36	17.8	12.72	14 (11-16)	
Radiotherapy						
Yes	109	74.14	28.44	19.44	17 (16-21)	<0.0001
No	86	38.82	10.78	5.39	11 (9-13)	
Leukopenia						
Grade I-II	131	66.49	23.54	14.27	16 (14-17)	0.4582
Grade III-IV	39	64.3	29.77	23.82	17 (12-23)	
First-line chemotherapy tumor response						
CR+PR	122	67.58	22.95	17	17 (15-18)	0.0326
SD+PD	51	48.9	14.68	0	11 (8-17)	

CEA, carcinoembryonic antigen; CR, complete response; CYFRA21-1, Cytokeratin fragments with MAbs BM19.21 and KS19.1; LDH, lactate dehydrogenase; NSE, neuron-specific enolase; PD, progressive disease; PR, partial response; SD, stable disease

Table 2. Simple and Multiple Cox Regression Model Evaluation of Prognostic Risk Factors

Variables	Simple model			Multivariate model	
	HR	95% CI	P	HR (95% CI)	P-value
Age	1.31	0.90, 1.91	0.1606	-	-
Gender	0.81	0.49, 1.34	0.4052	-	-
Smoke	0.89	0.58, 1.39	0.6212	-	-
Hemoglobin	1.94	1.12, 3.36	0.0188	-	-
Platelets	0.94	0.56, 1.57	0.8193	-	-
Albumin	0.58	0.32, 1.07	0.0837	-	-
LDH	1.13	0.72, 1.76	0.6003	-	-
NSE	1.46	0.89, 2.39	0.134	-	-
CEA	1.17	0.77, 1.80	0.4629	-	-
CYFRA21-1	1.54	0.98, 2.42	0.0625	-	-
Liver metastasis	2.31	1.57, 3.41	0	2.52 (1.69, 3.76)	<0.0001
Second-line chemotherapy	0.68	0.46, 1.01	0.0531	-	-
Radiotherapy	0.48	0.33, 0.70	0.0001	-	-
Leukopenia	0.79	0.48, 1.31	0.3635	-	-
First-line chemotherapy tumor response	1.61	1.04, 2.50	0.0324	-	-
Cycles of first-line chemotherapy	0.82	0.73, 0.92	0.0011	-	-
Number of cycles of all chemotherapy	0.86	0.80, 0.93	0.0001	0.86 (0.80-0.92)	<0.0001

CEA, carcinoembryonic antigen; CYFRA21-1, Cytokeratin fragments with MAbs BM19.21 and KS19.1; HR, hazard ratio; DH, lactate dehydrogenase; NSE, neuron-specific enolase

radiotherapy or second-line chemotherapy. A 3-year survival benefit was also associated with tumor response to first-line chemotherapy (complete or partial response vs progress or stable disease, P=0.0369) and levels of hemoglobin (normal vs low, P=0.0173) (Table 1).

Multivariate analysis identified the presence of liver metastasis and the total number of all chemotherapy cycles as independent factors for prognosis (Table 2). The morbidity risk for patients with liver metastasis was 2.52-fold higher than the morbidity risk for patients without liver metastasis (hazard ratio [HR]; [95% confidence interval (CI)]; 2.52 [1.69-3.76]; P < 0.0001). A one unit increase in the total number of chemotherapy cycles decreased the risk of death by 0.86-fold (HR 0.86; CI [0.80-0.92]; P < 0.0001).

In this study, common treatment-related side effects included nausea, vomiting, and diarrhea, as well as bone marrow suppression. There were no treatment-related deaths.

Discussion

The proportion of SCLC patients diagnosed with ES-SCLC has increased to 75%; however, the prognosis has changed very little over the past 30 years (Neal et al., 2011). The median survival of ES-SCLC patients is 10 months, and only 2% survive 5 years beyond the cancer diagnosis (Neal et al., 2011). The tumors in most patients with ES-SCLC will eventually progress (after an initial response to chemotherapy), and the patient will succumb to the cancer. Our study suggests the lack of liver metastasis and the ability of a patient to receive and tolerate multiple lines of chemotherapy were associated with longer survival

Studies have suggested various factors influence treatment results, disease progression, and long-term survival in patients with SCLC (Fizazi et al., 1998; Paesmans et al., 2000; Ando et al., 2004; Singh et al., 2005; Ustuner et al., 2008; Ou et al., 2009). In this study, survival in patients with ES-SCLC was associated with liver metastasis, second-line chemotherapy, radiotherapy, normal initial levels of hemoglobin, and tumor response to first-line chemotherapy. The presence of liver metastasis and the total number of all chemotherapy cycles were found to be independent predictors of survival.

The identification of liver metastasis as a significant prognostic indicator is consistent with a prior study (Bremnes et al., 2003); however, another study suggested multiple metastatic sites indicated a poor prognosis for survival but established no association of the liver metastasis with survival (Ou et al., 2009). The number of metastatic sites generally reflects the extent of disease, which has consistently been found to be a prognostic factor for survival (Paesmans et al., 2000; Bremnes et al., 2003; Li et al., 2010). In this study, the relationship between multiple metastatic sites and survival was not evaluated.

In this study, 85 (42.5%) patients received second-line chemotherapy, while 105 patients (52.5%) received palliative care. Prior trials have found that maintenance therapy beyond six cycles of first-line therapy did not increase survival in patients whose tumors responded to the initial therapy (Sørensen et al., 2010). However, patients who were treated with second-line therapy following relapse had some survival benefit (O'Brien et al., 2006; Sørensen et al., 2010). We found a survival benefit for patients treated with second-line therapy and no association of the number of first-line cycles with survival. Multivariate analysis showed that a greater number of chemotherapy cycles (including first, second, and third-line) was associated with longer survival. Tumor response to first-line chemotherapy was associated with survival.

These guidelines consider that only a subgroup of patients with ES-SCLC are potential candidates for second-line chemotherapy and should be selected on the basis of response to first-line treatment, time interval since discontinuation of first-line treatment, residual toxicity to first-line therapy, and performance status, as these parameters have been found to influence survival (Sørensen et al., 2010). It is possible that patients in our study who had a survival benefit from an increased number of chemotherapy cycles may have represented a subgroup of patients with specific disease characteristics that allowed them to tolerate the extra treatment and have an increased survival.

Prior studies have identified a number of prognostic markers for survival of ES-SCLC, although the results have been inconsistent (Paesmans et al., 2000; Ando et al., 2004; Ou et al., 2009). Similar to our results, some studies have found the level of hemoglobin was associated with survival (Bremnes et al., 2003). However, in contrast to our results, studies have found that factors including age, gender, smoking history, platelet count, and levels of albumin, LDH, NSE, CEA, and CYFRA21-1 were potential prognostic factors for survival (Ando et al., 2004; Singh et al., 2005; Ou et al., 2009). Yang et al. (2011) reported that CEA, but not tumor stage, was an independent prognostic factor negatively correlated with overall survival in Chinese SCLC patients. Reasons for discrepancies between our study and other studies may

reflect different methods for measuring survival and different sample sizes and study designs. Other factors that were not investigated in this study but have been indicated as possible prognostic factors include levels of VEGF, performance status, Asian ethnicity, socioeconomic status, weight loss, neutrophil count, and white blood cell levels (Paesmans et al., 2000; Ustuner et al., 2008; Li et al., 2010).

A subset of patients in this study received radiotherapy to the chest, bone, or brain in addition to chemotherapy. We found that radiotherapy was associated with improved survival, which is consistent with previous studies. In a randomized trial, the combination of chemotherapy and thoracic radiotherapy compared with chemotherapy alone resulted in a median 5-year survival rate of 9.1% versus 3.7%, respectively, for patients with ES-SCLC (Jeremic et al., 1999). In another randomized study, prophylactic cranial irradiation reduced the risk of symptomatic brain metastases and also improved survival in patients with ES-SCLC (Slotman et al., 2007).

This study was a single site, retrospective study with a small sample size. Larger prospectively designed multi-institutional studies are required to further address what factors are prognostic for survival in ES-SCLC.

In this study, we found that the lack of liver metastasis and the ability of a patient to receive and tolerate multiple lines of chemotherapy were associated with longer survival.

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