Long-Term Survival in Extensive Disease Small Cell Lung Cancer Patients Treated Without Immune Checkpoint Inhibitors

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Abstract

Background: Immune checkpoint inhibitors (ICIs) combined with chemotherapy have been approved as first-line treatment for patients with untreated extensive disease-small cell lung cancer (ED-SCLC). However, there are few reports about the long-term survival in patients with ED-SCLC treated without ICIs. Thus, we analyzed the long-term survival in patients with ED-SCLC.

Methods: We retrospectively examined the medical records of patients with SCLC who were treated at our hospital between September 2002 and September 2019. The main inclusion criteria were as follows: (1) histological or cytological confirmation of SCLC, (2) diagnosed with ED-SCLC, and (3) received chemotherapy, not including ICIs, as the first-line treatment. To assess the trends of treatment outcomes, we compared the survival outcomes between 2002–2010 (early) and 2011–2019 (late) groups.

Results: A total of 314 patients were included in this study. Patient characteristics at the time of first-line treatment were as follows: median age was 69 years; 82% of the patients were male; and 70% had a performance status of 0 or 1. The median follow-up time of overall survival (OS) was 7.4 years, and 89% of the patients died. The median progression-free survival and survival time were 4.9 months and 12.1 months, respectively. Five-year survival rate was 2%. There was no significant difference in survival between the early and late groups.

Conclusion: We found that the long-term survival in ED-SCLC patients treated without ICIs was poor. Prior to the approval of ICI treatment for ED-SCLC, there was no improvement in the OS for approximately 20 years.

Background

Lung cancer is the most common cause of cancer-related deaths worldwide. Small-cell lung cancer (SCLC) is one of the major histological types of lung cancers and accounts for 10%–15% of all lung cancers[1]. Approximately 60%–70% of patients have extensive disease (ED)-SCLC, with a poor prognosis. Although SCLC shows high sensitivity to chemotherapy and radiotherapy, the median survival time (MST) for ED-SCLC is 8–13 months, and the two-year survival rate is only 5%[2]. In the recent decades, no drug has shown promising results in improving the prognosis of patients with ED-SCLC.

In 2015, nivolumab monotherapy for patients with non-small-cell lung cancer (NSCLC) showed better survival benefits than chemotherapy[3,4]. Subsequently, many phase III trials that evaluated the efficacy of immune checkpoint inhibitors (ICIs) demonstrated their clinical benefit in patients with NSCLC[5-9]. Consequently, four drugs, nivolumab, pembrolizumab, atezolizumab, and durvalumab, have been currently approved for patients with NSCLC. In case of SCLC, the efficacy of ICIs has not been reported by many trials in several years. However, the IMpower 133 trial, conducted in 2018[10], compared carboplatin, etoposide, and atezolizumab with carboplatin, etoposide, and placebo for patients with previously untreated ED-SCLC, with investigator-assessed progression-free survival (PFS) and overall survival (OS) as the primary endpoints. The median PFS (mPFS) was 5.2 months in the atezolizumab

group and 4.3 months in the placebo group (hazard ratio [HR]: 0.77, 95% confidence interval [CI]: 0.62–0.96, $p = 0.02$), and the MST was 12.3 months and 10.3 months, respectively (HR: 0.70, 95% CI: 0.54–0.91, $p = 0.007$). IMpower 133 showed that the addition of atezolizumab to chemotherapy significantly prolonged PFS and OS compared with chemotherapy alone. The CASPIAN study, a phase III study of durvalumab conducted in 2019, was designed similar to the IMpower 133 trial and reproducibly showed that the addition of ICI to chemotherapy was also effective in patients with ED-SCLC. Based on these two studies, many guidelines recommend atezolizumab or durvalumab combined with chemotherapy as first-line treatment for patients with ED-SCLC.

Recently, clinical trials that compared ICI monotherapy with docetaxel for NSCLC patients[11-13] reported long-term survival results, which were represented by a plateau in the right tail of the survival curve. However, the median follow-up period of the trial that evaluated the efficacy of ICI combined with cytotoxic chemotherapy in patients with NSCLC or ED-SCLC was approximately 2 years, and it is unclear whether ICI combined with cytotoxic chemotherapy shows a plateau in the right tail of the survival curve. Although the data on long-term survival in patients with ED-SCLC treated without ICIs are necessary to assess the efficacy of ICIs combined with chemotherapy, there are limited reports documenting these data.

Methods

2.1. Patients

We retrospectively analyzed data on consecutive patients with ED-SCLC treated with first-line chemotherapy between September 2002 and June 2019 from the medical records of Shizuoka Cancer Center. The recruitment criteria for this study were as follows: (1) histological or cytological confirmation of SCLC, (2) diagnosis of ED-SCLC, (3) received chemotherapy, not including ICIs, as the first-line treatment, and (4) no history of interstitial lung disease. We defined sensitive relapse as treatment-free interval ≥ 90 days.

To assess the trends of treatment outcomes, we divided the patients with ED-SCLC into two groups according to the year of the first-line treatment. The “early group” included patients treated during 2002–2010 and the “late group” included patients treated during 2011–2019.

2.2 Evaluation and statistical analysis

We evaluated the tumor response to chemotherapy in accordance with the Response Evaluation Criteria in Solid Tumors by performing chest and abdomen computed tomography, head magnetic resonance imaging, bone scintiscan, or positron emission tomography–computed tomography[14]. All categorical variables were analyzed using the chi-square test or Fisher’s exact test, as appropriate. Clinical evaluation of PFS and OS after the initiation of first-line chemotherapy was conducted using the Kaplan–Meier method to assess the time of recurrence or death, respectively. Survival analyses were performed using the log-rank test. The follow-up period was also estimated using the Kaplan–Meier method. All tests were

two-sided, and p-values < 0.05 were considered significant. Statistical analyses were performed using the JMP software version 9.0 (SAS Institute Inc., Cary, NC) and EZR. The data cutoff date was June 30, 2020. Our study was approved by the Institutional Review Board of the Shizuoka Cancer Center.

Results

3.1. All patients

3.1.1 Patient characteristics

Between September 2002 and June 2019, a total of 314 patients with ED-SCLC were included in this study. Patient characteristics at the time of first-line treatment were as follows: median age was 69 (range, 43–89) years; 82% of the patients were males, 70% had a performance status (PS) of 0 or 1, 97% were past or current smoker, 98% had stage IV disease, and 34% of the patients had brain metastasis (Table 1).

Table 1
Patient characteristics during first-line treatment

	Number of patients (n = 314)
Age (years)	
Median	69
Range	43–89
≥ 75, n (%)	74 (24)
Gender, n (%)	
Male	258 (82)
Female	56 (18)
PS at first-line treatment, n (%)	
0–1	221 (70)
2–4	93 (30)
Stage at diagnosis, n (%)	
stage IV	308 (98)
Other	6 (2)
Smoking Status, n (%)	
Current or Former	306 (97)
Never	6 (2)
Unknown	2 (1)
Metastatic site, n (%)	
Lung	53 (17)
Pleural effusion or dissemination	108 (34)
Brain	108 (34)
Liver	85 (27)
Bone	90 (29)
Adrenal gland	57 (18)

Abbreviations: PS: performance status

	Number of patients (n = 314)
Regimen of first-line treatment, n (%)	
Cisplatin plus Etoposide	39 (12)
Cisplatin plus Irinotecan	87 (28)
Carboplatin plus Etoposide	155 (49)
Other	33 (11)
Subsequent chemotherapy, n (%)	
Yes	222 (71)
No	92 (29)
Relapse pattern of patients treated with subsequent systemic therapy, n (%)	
Sensitive relapse	157 (50)
Refractory relapse	65 (21)
Abbreviations: PS: performance status	

Carboplatin plus etoposide was the most commonly used drug and was administered to 155 patients (49%) while cisplatin plus irinotecan and cisplatin plus etoposide were administered in 28% and 12% of the patients, respectively. Subsequent chemotherapy was administered in 222 patients (71%) and amrubicin was most frequently administered drug.

3.1.2. Efficacy

The overall response rate (ORR) of first-line treatment was 80% in all patients with ED-SCLC (Table 2).

Table 2
Best response to first-line treatment

	Number of patients (N = 314)	Early group (N = 127)	Late group (N = 187)
Best response, n (%)			
CR	6 (2)	3 (2)	3 (2)
PR	245 (78)	96 (76)	149 (80)
SD	26 (8)	8 (6)	18 (10)
PD	16 (5)	7 (5)	9 (5)
NE	21 (7)	13 (11)	8 (4)
Response rate (%)	80	78	81
p-value		0.470	
Abbreviations: CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, NE: not evaluable			

The median follow-up time for OS was 7.4 years (95% CI: 4.7–8.9 years), and event was observed in 280 patients (89%). MST and mPFS was 12.1 months (95% CI: 10.8–13.1 months) and 4.9 months (95% CI: 4.6–5.2 months), respectively (Figure 1). One-year, two-year, three-year, and five-year survival rates were 49%, 14%, 6%, and 2%, respectively. MST in patients with PS of 0-1, who seemed to be included in the IMpower133 trial, was 13.4 months and five-year survival rate was only 3%.

3.2. Early group and late group

3.2.1. Patient characteristics

In total, 127 and 187 patients were grouped into the early and late groups, respectively. There was no significant difference in gender, PS at first-line treatment, and smoking status between the two groups (Table 3).

Table 3
Patient characteristics in the early and late groups

	Early Group (n = 127)	Late Group (n = 187)	p-value
Age (years)			
Median	67	70	
Range	43–86	51–89	0.017
≥ 75, n (%)	27 (21)	47 (25)	0.4273
Gender, n (%)			
Male	105 (83)	153 (82)	
Female	22 (17)	34 (18)	0.845
PS at first-line treatment, n (%)			
0–1	90 (71)	131 (70)	
2–4	37 (29)	56 (30)	0.877
Stage at diagnosis, n (%)			
stage IV	122 (96)	186 (99)	
Other	5 (4)	1 (1)	0.031
Smoking Status, n (%)			
Current or Former	123 (97)	183 (97)	
Never	3 (2)	3 (2)	
Unknown	1 (1)	1 (1)	0.856
Metastatic site, n (%)			
Lung	32 (25)	21 (11)	0.001
Pleural effusion or dissemination	46 (36)	62 (33)	0.575
Brain	44 (35)	64 (34)	0.939
Liver	31 (24)	54 (29)	0.382
Bone	37 (29)	53 (28)	0.879
Adrenal gland	22 (17)	35 (19)	0.753
Abbreviations: PS: performance status			

	Early Group (n = 127)	Late Group (n = 187)	p- value
Regimen of first-line treatment, n (%)			
Cisplatin plus Etoposide	14 (11)	25 (13)	
Cisplatin plus Irinotecan	44 (35)	43 (23)	
Carboplatin plus Etoposide	51 (40)	104 (56)	
Other	18 (14)	15 (8)	0.015
Subsequent chemotherapy, n (%)			
Yes	95 (75)	127 (68)	
No	32 (25)	60 (32)	0.395
Relapse pattern of patients treated with subsequent systemic therapy, n (%)			
Sensitive relapse	30 (24)	35 (19)	
Refractory relapse	65 (51)	92 (49)	0.515
Abbreviations: PS: performance status			

Although the proportion of patients over 75 years old was not significantly different, more older patients were included in the late group. The proportion of patients with stage IV disease or lung metastasis was greater in the late group. Subsequent chemotherapy was administered in 75 patients (75%) of the early group and 127 patients (68%) of the late group.

3.2.2. Efficacy

The ORR of first-line treatment was 78% in the early group and 81% in the late group (Table 2). The MST was 13.0 months (95% CI: 10.5–14.6 months) in the early group, versus 11.8 months (95% CI: 9.4–12.9 months) in the late group ($p = 0.18$, Figure 2A). The mPFS was 4.9 months (95% CI: 4.2–5.5 months) and 4.9 months (95% CI: 4.6–5.2 months) in the early and late groups ($p = 0.87$, Figure 2B), respectively.

Discussions

In this study, we retrospectively analyzed the long-term survival of first-line treatment in patients with ED-SCLC. Our study showed that the MST of first-line treatment was 12.1 months and the five-year survival rate was only 2%. There was no significant difference in survival when comparing the treatment outcomes from 2002 to 2010 with those from 2011 to 2019. The efficacy of first-line treatment with chemotherapy alone in patients with ED-SCLC is still poor, and there has been no improvement in survival for approximately 20 years.

Only a few drugs for SCLC patients have been approved in the last 20 years and cisplatin plus etoposide or irinotecan have been the standard treatment until recently. ICIs, such as atezolizumab and durvalumab, were approved as first-line treatment for ED-SCLC patients in 2019. The follow-up period of the studies that led to the approval of ICIs for patients with ED-SCLC were short, and there are limited reports on the long-term survival of ED-SCLC patients treated without ICIs. In 1995, the long-term survival of 1714 patients with SCLC were reported from nine trials[15]. This report included 886 ED-SCLC patients, and the five-year survival rate was 2.3%; these results were comparable with our results. Schabath et al. reported temporal trends from 1986 to 2008 in SCLC patient survival[16]. They divided 1032 patients with ED-SCLC into two groups based on the year of treatment: patients treated between 1986 and 1999 and those treated between 2000 and 2008. The five-year survival rate was significantly higher in the 2000–2008 time-period (8.3% vs. 11.0%, $p < 0.001$). MST increased from 11.3 months to 15.2 months between the two groups. On the other hand, Lattuca-Truc et al. reported trends in survival of SCLC patients between 1997 and 2017[17]. They included 529 patients with SCLC and compared survival between 1997-2009 (period 1) and 2010-2017 (period 2). MST was 13.2 months in period 1 and 11.2 months in period 2. Treatment period was not an independent factor associated with death when analyzed by multivariate analysis (HR: 0.82, 95% CI: 0.66–1.00). Oze et al. reported trends in SCLC in 1993-2006 based on Population-Based Cancer Registry data[18]. They showed that prognosis of patients with SCLC plateaued from 1999-2001 to 2002-2006. These results suggest that treatment outcomes have not improved since 2000. Patients treated from 2002 to 2019 were included in our study, and there was also no significant difference in treatment outcomes by year with chemotherapy as first-line treatment. Because our study included patients who were treated just before the ICIs was approved, we think our results was an important reference for future studies evaluating the efficacy of ICIs combined with chemotherapy in ED-SCLC patients.

In case of NSCLC, studies have revealed that ICI monotherapy shows a plateau in the right tail of the survival curve. However, cytotoxic chemotherapy did not show a plateau, and the survival rate was close to zero. When ICI was combined with chemotherapy, it was unclear whether it shows a plateau in the right tail of the survival curve because of the short follow-up period of the study, while our study showed the long-term survival of patients with ED-SCLC without treatment with ICIs. We believe our study will be an important reference for future studies on ICIs combined with chemotherapy for patients with ED-SCLC.

Our study had several limitations. First, the sample size was small and this study was the result of a single-center analysis. However, our study included only patients with ED-SCLC, and there are only a few reports on ED-SCLC patients. Moreover, our study had a follow-up time of almost 7 years, which was longer than the average time-period of previous clinical trials. Based on these factors, we believe our study is very worthwhile. Second, the timing of response assessment was decided by each physician; although, this might have introduced variance of ORR and PFS, we also assessed OS, which was a reliable endpoint. Finally, this study was retrospective analysis. However, a prospective study assessing the long-term survival of patients with ED-SCLC treated without ICI is difficult. We thought our results were important as real-world data of those patients. For more reliable data of long-term survival in patients with ED-SCLC, multi institutional study of ED-SCLC was warranted in the future.

Conclusion

In conclusion, this study revealed that the long-term survival in patients with ED-SCLC treated without ICI was poor. Analysis of the survival trend for patients with ED-SCLC prior to the approval of ICI treatment revealed no improvement in patient survival. We believe our study will be an important reference for future studies evaluating the efficacy of ICIs combined with chemotherapy in ED-SCLC patients.

Abbreviations

SCLC: small cell lung cancer, ED: extensive disease, MST: median survival time, NSCLC: non-small-cell lung cancer, ICI: Immune checkpoint inhibitor, PFS: progression-free survival, OS: overall survival, mPFS: median progression-free survival, HR: hazard ratio, CI: confidence interval, PS: performance status, ORR: overall response rate

Declarations

Authors' contributions: KW conceived the study. Analyses were performed by KW. MY, HK, NN, TM, EM, NM, HK, and SO reviewed the results and discussion. KW wrote the paper with contributions from AO, HK, TN, HM, TS, YG, and TT. This article is an original research work, and all authors have read and approved the final version of the manuscript

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Ethics approval and consent to participate: Our study was approved by the Institutional Review Board of the Shizuoka Cancer Center. The need to obtain informed consent to participate was waived due to the retrospective design of this study.

Consent for publication: Not applicable

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Figures

Figure 1A

Figure 1B

Figure 1

(A) Overall Survival, and (B) progression-free survival of patients with extensive disease small cell lung cancer

Figure 2A

Figure 2B

Figure 2

(A) Overall Survival, and (B) progression-free survival in the early and late groups.