Efficacy of Definite Concurrent Chemoradiotherapy for Patients with Limited-Disease Small-Cell Lung Cancer: A Retrospective, Nationwide, Population-Based Cohort Study

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Abstract

Background: Small-cell lung cancer (SCLC) is a highly proliferative, rapidly growing tumor with a poor prognosis, even in cases of limited disease (LD). Timely and accurate high-intensity therapy is necessary. For concurrent chemoradiotherapy (CCRT), etoposide/platinum (EP)-based regimens are recommended, although irinotecan/platinum (IP)-based regimens are also effective with radiotherapy. This large-scale, retrospective, nationwide cohort study aimed to analyze the efficacy of CCRT in patients with LD-SCLC.

Methods: Population data registered between January 2008 and December 2018 were extracted from the Health Insurance Review and Assessment Service of Korea database. Survival outcomes of 4,446 LD-SCLC patients who received CCRT were analyzed.

Results: Patients who received EP-CCRT ($n = 4,187$) showed better progression-free survival (PFS: 11.2 months) and overall survival (OS: 22.2 months) than did those who received IP-CCRT ($n = 259$; PFS: 9.6 months, $P = 0.0477$; OS: 16.4 months, $P < 0.0001$). When CCRT failed, dual-agent chemotherapy ($n = 925$; OS: 9.1 months) provided a better survival benefit than did single-agent chemotherapy ($n = 815$; OS: 7.5 months). IP-based chemotherapy resulted in better OS (9.6 months) than did EP-based chemotherapy (7.1 months, $P = 0.0170$) in platinum-resistant relapsed patients; the opposite was observed for platinum-sensitive relapsed patients (OS: EP, 17.2 months; IP, 6.6 months; $P < 0.0001$). Cox proportional hazards regression analysis demonstrated that age, EP-CCRT, and hypercholesterolemia retained significant associations with OS after adjustment for all variables.

Conclusion: In the Korean population, the effects of EP-CCRT on OS and PFS are significantly more favorable than those of IP-CCRT.

Background

Small-cell lung cancer (SCLC) is an aggressive lung cancer subtype that accounts for only 12–15% of all lung cancer diagnoses [1, 2]. At diagnosis, approximately a third of patients have limited-disease (LD) SCLC. The limited-stage disease is confined to the ipsilateral hemithorax or mediastinal or supraclavicular lymph nodes, which can be safely encompassed within a radiation field; whereas, metastatic tumors are categorized under extensive-disease (ED) SCLC [1]. For LD-SCLC, the median survival and 2-year survival rate have been assessed to be 15–20 months and 20–40%, respectively. Importantly, the proportion of patients who survive for 5 years is reportedly only 14–26% [2]. Although LD-SCLC is a potentially curable disease, it exhibits a high histological proliferation rate and clinically varied manifestations such as paraneoplastic syndromes; therefore, any wastage of time can result in a change in the treatment modality and worsen the prognosis [2, 3].

Almost two decades ago, the addition of twice-daily radiotherapy to combination chemotherapeutic agents was the cornerstone of LD-SCLC treatment [4, 5], with the strategies significantly improving the survival of patients with LD-SCLC. In the era of immunotherapy, there has been a paradigm shift in the treatment of SCLC [6, 7]; however, concurrent chemoradiotherapy (CCRT) remains the current standard treatment worldwide [2, 3]. In previous studies, the overall response rate after CCRT reached $\geq 80\%$, with a complete remission rate of up to 45% [8, 9]. A large proportion of patients died from recurrence and distant metastasis. These findings result in constantly unmet needs for the development of chemotherapeutic agents and combinations that exhibit

greater antitumor effects and superior radiosensitization. CCRT based on an etoposide/platinum (EP)-based regimen has been the standard protocol since the early 1990s. In addition, an irinotecan/platinum (IP)-based regimen with radiation treatment has been reported to be effective and tolerable for patients with untreated LD-SCLC [10, 11]. Although several studies have verified the effectiveness of the two regimens in cases of LD-SCLC with similar schemes [8, 10–15], to our knowledge, no large-scale study has included LD-SCLC patients from an East Asian population. Therefore, we conducted a nationwide study to analyze the efficacy of definite CCRT in a large population of Korean patients with LD-SCLC using data from the Health Insurance Review and Assessment Service (HIRA) database. Korean health insurance covers the entire population of Korea, and HIRA provides information on healthcare services provided to the Korean population. Thus, by using the HIRA database, we could approach the entire Korean population.

Methods

Ethical statement

This study was approved by the Institutional Review Board of the Uijeongbu St. Mary Hospital, College of Medicine, Catholic University of Korea [UC18ZESI0145], and it conforms to the provisions of the Helsinki Declaration as revised in 2013 (available at: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>). The need for informed consent was waived because of the retrospective nature of the study.

Study design and population

To verify the reliability of the operational criteria for SCLC staging, we used single-institution data from 357 SCLC patients with known disease status. Using these operational criteria, patients with LD-SCLC were predicted with a sensitivity of 64.6%, specificity of 100%, and accuracy of 88.5% (Supplementary Table 2). This operational definition facilitates identification of most cases of LD-SCLC and completely rules out ED. Thus, these definitions can be used to specifically select patients with LD-SCLC. The median survival time of LD-SCLC patients was 21.8 months (95% confidence interval [CI], 20.86–22.96), defined per our operational criteria, while that of ED-SCLC patients was 9.6 months (95% CI, 9.43–9.83; Supplementary Fig. 1). The corresponding 5-year survival rates were $24.73 \pm 0.75\%$ and $8.13 \pm 0.30\%$, respectively. These findings were comparable with those for patients with LD-SCLC and ED-SCLC in recent studies [2, 16, 17]. Thus, our operational criteria were considered acceptable.

Definition of survival outcomes

The primary objective was to evaluate the survival outcomes of LD-SCLC patients after CCRT. Progression-free survival (PFS) was defined as the time from the date of first-line chemotherapy to the time of subsequent chemotherapy or death from any cause, whichever was earlier. Overall survival (OS) was calculated as the time from the date of diagnosis to the date of death or the last follow-up visit. The date of diagnosis was defined as the date of initiation of the first chemotherapy, surgery, or radiotherapy after the first-ever application of the C34 diagnostic code. For the patients who received second-line chemotherapy, OS was calculated from the start date of the second-line chemotherapy regimen to the date of death or the last follow-up visit.

Statistical analysis

Concerning baseline characteristics, continuous variables were processed as means ($\pm$ standard errors) or medians (range), while categorical variables were expressed as frequencies (%). A *t*-test was used for comparisons of continuous variables, and Pearson's chi-square test or the two-sample proportion *z*-test was used for comparisons of categorical variables. Cox proportional hazards regression analysis was performed to identify the risk factors for overall mortality. Survival curves were generated using the Kaplan–Meier method and compared using the log-rank test. The SAS Enterprise Guide version 6.1 (SAS Inc., Cary, NC, USA), Python 3.74 (Python Software Foundation), Visual Basic for Applications 7.0 (Microsoft Inc., Redmond, WA, USA), and Excel 2010 (Microsoft Inc.) were used for all data mining and statistical analyses.

Results

Baseline characteristics

A total of 4,446 patients were included in our study. The baseline characteristics of the patients are summarized in Table 1. The mean age was 64 years, and 85.4% of patients were male. In total, 2,187 (49.2%) patients were young (<65 years) while 2,259 (50.8%) were elderly (≥ 65 years). Concerning CCRT, 4,187 (94.2%) and 259 (5.8%) received EP-CCRT and IP-CCRT, respectively. Second-line treatment was received by 1,740 patients because of the failure of definite CCRT or progression during treatment; 925 (53.2%) received combination chemotherapy, and 815 (46.8 %) received single-agent chemotherapy.

Clinical outcomes of definite CCRT and second-line treatment

Median PFS was significantly longer with EP-CCRT (11.2 months, 95% CI: 10.90–11.67) than with IP-CCRT (9.6 months, 95% CI: 8.50–10.67; $P = 0.0477$; Fig. 2A). OS was also significantly longer with EP-CCRT (22.2 months, 95% CI: 21.23–23.33) than with IP-CCRT (16.4 months, 95% CI: 14.47–18.33; $P < 0.0001$; Fig. 2B). Among patients who received second-line chemotherapy, those who received combination chemotherapy showed a better survival benefit (9.1 months, 95% CI: 8.40–10.10) than did those who received monotherapy (7.5 months, 95% CI: 6.93–8.13; $P < 0.0001$; Fig. 3A). Concerning the combination chemotherapy regimens, the EP combination resulted in significantly better OS (11.2 months, 95% CI: 8.87–13.27) than did the IP combination (8.9 months, 95% CI: 8.23–9.67; $P = 0.0128$; Fig. 3B). However, there were no significant differences in OS among single-agent regimens used for second-line treatment ($P = 0.3712$; Supplementary Fig. 2).

Clinical outcomes of second-line treatment according to PFS of <6 months or >6 months after CCRT

Patients who received second-line treatment were classified into platinum-resistant and platinum-sensitive relapsed groups according to PFS of <6 months and >6 months after CCRT, respectively. In the platinum-resistant relapsed group, second-line IP-based chemotherapy resulted in significantly better OS (9.6 months, 95% CI: 8.67–10.33) than did second-line EP-based chemotherapy (7.1 months, 95% CI: 5.10–10.40; $P = 0.0170$; Supplementary Fig. 3A). Conversely, second-line EP-based chemotherapy (OS: 17.2 months, 95% CI: 13.03–25.63) was superior to second-line IP-based chemotherapy (OS: 6.6 months, 95% CI: 5.43–7.77; $P < 0.0001$; Supplementary Fig. 3B) in the platinum-sensitive relapsed group.

Factors associated with survival outcomes in patients with LD-SCLC

The results of univariate and multivariate analyses of risk factors for poor survival in patients with LD-SCLC are listed in Table 2. Univariate analysis demonstrated that older age, the male sex, the presence of hypertension, the absence of hypercholesterolemia, and the use of IP-CCRT as definite treatment were significantly associated with shorter OS. In the multivariate analysis, variables that were significantly associated with poor survival included older age (adjusted hazard ratio [HR]: 1.64, 95% CI: 1.45–1.85; $P < 0.0001$), the absence of hypercholesterolemia (adjusted HR: 1.23, 95% CI: 1.10–1.39; $P < 0.0001$), and the use of IP-CCRT as definite treatment (adjusted HR: 19.47, 95% CI: 6.13–61.77; $P < 0.0001$).

Discussion

In the present population-based study, we investigated the efficacy of definite CCRT using real-world data for patients with LD-SCLC. The results revealed that the survival outcomes patients who received EP-CCRT were better than those patients who received IP-CCRT. As second-line treatment in cases of CCRT failure or progression during treatment, the EP regimen resulted in better OS than did the IP regimen; however, the IP regimen was more effective in patients with PFS of <6 months after CCRT, i.e., platinum-resistant relapsed patients. This study provides evidence that the EP combination should be the gold standard for CCRT in Korean patients with LD-SCLC. To the best of our knowledge, this analysis included the largest study population till date.

Previous studies have provided sufficient evidence for the advantages of the EP regimen over other regimens for CCRT [2, 5, 9]. EP-based chemotherapy, combined with concurrent thoracic radiotherapy, has been considered the standard of care for patients with LD-SCLC, with lesser toxic effects on intrathoracic organs and the ability for radiosensitization [9]. Previous randomized trials have suggested that concurrent thoracic radiotherapy and EP-based chemotherapy is better than older regimens such as doxorubicin-based or cyclophosphamide-based ones [9, 18]. Despite a better response to chemotherapy alone, doxorubicin-based or cyclophosphamide-based CCRT showed a median OS period of just 15 months in patients with LD-SCLC. These unsatisfactory results may be partially attributed to significant toxic effects such as more myelosuppression, weight loss, esophagitis, and pulmonary dysfunction [9, 19, 20].

In a recent randomized trial including a Korean population, IP-based chemotherapy had significantly favorable effects on survival outcomes when compared to EP-based chemotherapy for previously untreated ED-SCLC [17]. Similar findings were reported in a meta-analysis of six trials involving 1,476 patients [21]. In addition to having cytotoxic effects on SCLC, irinotecan is known to be a potent radiosensitizing agent [22], and the IP combination has been adopted as the chemotherapy regimen in CCRT for LD-SCLC. Although it has been shown that IP-based chemoradiotherapy is effective and tolerable in Asian and Western populations, there has been no direct comparison between EP-CCRT and IP-CCRT. Table 3 summarizes the results of previous studies on EP-CCRT and IP-CCRT for LD-SCLC. In a nutshell, the efficacy of IP-CCRT was comparable to that of EP-CCRT in patients with untreated LD-SCLC. The results of phase II trials showed that median survival with IP-based CCRT was 12.4–44.5 months, which was comparable to the survival time with EP-CCRT; however, there were considerable discrepancies in results among different studies [4, 8, 10–15, 23]. In a phase II study in

Japan, IP-based chemotherapy with concurrent split-course radiotherapy showed a remarkable survival benefit, with a median time to progression of 14.5 months and a median OS duration of 44.5 months [11]. However, in a phase II trial in Korean patients with LD-SCLC, median OS was 20.0 months, with 1-year and 2-year OS rates of 85% and 35%, respectively [23]. Similarly, in a western phase II trial, the overall radiographic response rate was 67%, median OS was 19 months, and the 1-year and 2-year OS rates were 60% and 44%, respectively [10].

However, these substantial differences in efficacy among studies on IP-based CCRT may be explained by differences in the timing of radiotherapy and its optimal dose, fractionation of thoracic radiotherapy, and consolidation chemotherapy. Pneumonitis and neutropenia were the main toxicities caused by IP-CCRT. Of note, pneumonitis is an important problem associated with IP-based chemoradiotherapy [20]. A study by Ohe et al. showed that pulmonary fibrosis identified on plain chest X-rays was a very strong risk factor for thoracic radiotherapy-related death [19], and that CCRT-related deaths occurred in 25 of 926 (2.7%) patients, including seven (28%) with radiation pneumonitis [19]. In the real-world setting, the rate of poor prognostic factors, the proportion of elderly patients, or the presence of comorbidities may be higher. Furthermore, patient compliance may be poorer, and routine medical practice may differ from protocol-specific patient care provided in clinical trials [24]. In the present study, patients who received EP-CCRT showed significantly better PFS and OS than did those who received IP-CCRT. Thus, treatment-related toxicities, including pulmonary toxicities, may have an unfavorable impact on the patients' clinical outcomes. Taken together, the EP regimen should be strongly considered as a concurrent chemotherapeutic regimen in definite CCRT for LD-SCLC.

Recently, Horn et al. demonstrated better PFS and OS when atezolizumab was added to chemotherapy for ED-SCLC than when only chemotherapy was used (OS, 12.3 vs. 10.3 months; PFS, 5.2 vs. 4.3 months) [6]. Of note, xenograft models have proved the synergistic effects of radiotherapy with immune checkpoint inhibitors [25], which are expected to have promising clinical efficacy through low toxicity and abscopal effects in several ongoing studies [NCT03811002, NCT02402920] regarding LD-SCLC.

Concerning the strategy of using cytotoxic chemotherapy as a second-line treatment for LD-SCLC, there is no consensus on the most effective regimen. In the present study, patients who received combination chemotherapy as a second-line treatment showed significantly better OS than did those who received single agents as second-line treatment; this finding is consistent with that of a previous study [26]. Multi-agent chemotherapy has historically demonstrated response rates higher than those shown by single-agent chemotherapy in cases of relapsed SCLC. However, these better rates have often been achieved with an increase in toxicities. A recent Japanese phase III trial demonstrated the superiority of the cisplatin, irinotecan, and etoposide combination over topotecan alone as a second-line regimen for platinum-sensitive relapsed SCLC (OS: 18.2 vs. 12.5 months, HR: 0.67, 95% CI: 0.51–0.88; $P = 0.0079$) [26]. However, it has been emphasized that this combination should be administered only in select patients, such as those with platinum-sensitive relapsed SCLC, because of associated toxicities.

Clinically, the differentiation of platinum-sensitive and platinum-resistant SCLC patients is essential. Although there are some reports about the association between the platinum sensitivity status and clinical outcomes in patients with relapsed SCLC, the role of the platinum sensitivity status remains controversial [27]. In a previous study, cross-administration of chemotherapy was effective in the platinum-resistant relapsed group [27]. In the

present analysis, we could confirm that IP-based chemotherapy resulted in better OS than did EP-based chemotherapy in platinum-resistant relapsed patients, defined by PFS of <6 months after CCRT.

Poor prognostic factors for patients with LD-SCLC included older age, the male sex, the absence of hypercholesterolemia, and the use of IP-CCRT as definite treatment. There are many conflicting reports about the prognostic role of lipidemia in cancer patients. Some studies have shown that malignant aerobic glycolysis, or the Warburg effect, leads to efficient biomass synthesis, including lipid synthesis, which is required for malignant cell proliferation [28]. In contrast, adipose tissue modulates the storage of extrinsic potential carcinogens such as benzo(a)pyrene, which induces DNA adduct formation and prevents the accumulation of carcinogen-DNA adducts in target organs, resulting in reduced cancer risk [29].

Hypocholesterolemia is often observed in patients with advanced-stage cancer, probably because of increased demand for cholesterol by neoplastic cells, which results in increased low-density lipoprotein cholesterol removal. This dynamicity is involved in the prognosis of SCLC, regulating the metabolism of lipids as dynamic organelles [30].

This study has several limitations that must be considered when interpreting the results. First, several potential information biases might exist. The HIRA data were retrospectively analyzed, and there was no information regarding the radiation dose, chemotherapy dose intensity, frequency of adverse treatment-related reactions, and causes of death. Second, identification of LD-SCLC or ED-SCLC patients as per the operational definition may be associated with bias. However, to overcome such bias, we used a strict multistep approach, and the Kaplan–Meier curves for LD-SCLC and ED-SCLC showed results similar to those in recent studies. Moreover, the clinical implications were validated through single-institute pooled analysis.

The results of this study suggest that the effects of EP-CCRT on OS and PFS are significantly more favorable than those of IP-CCRT in Korean patients with LD-SCLC. In cases where CCRT fails, combination chemotherapy provides a better survival benefit than does single-agent chemotherapy. Moreover, in CCRT failure cases with PFS of <6 months (platinum-resistant relapsed patients), IP-based chemotherapy has significantly better effects on OS and PFS than does EP-based chemotherapy.

Abbreviations

SCLC

Small-cell lung cancer; LD:limited disease; CCRT:concurrent chemoradiotherapy;EP:etoposide/platinum; IP:irinotecan/platinum; PFS:progression-free survival; OS:overall survival; ED:extensive-disease; HIRA:Health Insurance Review and Assessment Service; ICD:International Classification of Diseases; NHIS:National Health Insurance Service; CI:confidence interval; HR:hazard ratio;

Declarations

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None.

Author's contributions

YHK and JSL generated conception of the work; JSL, YHK, JHH, YHK, HWL, SRK, SYS got acquisition, analysis, and interpretation of the data; YHK, JSL, SRK have drafted the work; and JSL, SRK, YHK substantially revised it. All authors reviewed the manuscript.

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Availability of data and materials

All data analysed during this study are included in this published article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors have no conflicts of interest to declare.

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Tables

Table 1. Demographic characteristics of 4,446 patients with limited-disease small-cell lung cancer who received definite concurrent chemoradiotherapy

Variables	LD stage (n = 4,446)
Age, years	64 ± 8.28
<65	2,187 (49.2)
≥65	2,259 (50.8)
Sex (male/female)	3,797 (85.4)/649 (14.6)
Comorbidities	
HBP	2,361 (39.1)
DM	1,334 (22.1)
Hypercholesterolemia	2,314 (38.3)
First-line therapy	
Combination CRT	
Etoposide/platinum	4,187 (94.2)
Irinotecan/platinum	259 (5.8)
Second-line therapy	
Combination therapy	
Etoposide/platinum	151 (8.7)
Irinotecan/platinum	774 (44.5)
Single-agent therapy	
Etoposide	1 (0.1)
Irinotecan	232 (13.3)
Belotecan	342 (19.6)
Topotecan	240 (13.8)

Values are presented as mean ± standard deviation or number (%).

LD limited disease; *HBP* hypertension; *DM* diabetes mellitus; *CRT* chemoradiotherapy.

Table 2. Risk factors for overall survival in 4,496 patients with limited-disease small-cell lung cancer

	Univariate		Multivariate	
	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
Age, years (≥ 65 vs. <65)	1.61 (1.45–1.82)	<0.0001	1.64 (1.45–1.85)	<0.0001
Sex (male vs. female)	1.17 (1–1.37)	0.05	1.16 (0.99–1.37)	0.06
HBP (HBP vs. normal)	1.09 (0.98–1.22)	0.12	1.08 (0.96–1.21)	0.22
DM (DM vs. normal)	1.05 (0.93–1.19)	0.41	1.06 (0.93–1.2)	0.41
Hypercholesterolemia (No vs. yes)	1.15 (1.03–1.28)	0.01	1.23 (1.10–1.39)	<0.0001
Definite CCRT (IP-CCRT vs. EP-CCRT)	26.55 (8.38–84.11)	<0.0001	19.47 (6.13–61.77)	<0.0001

HR, hazard ratio; *CI*, confidence interval; *HBP*, hypertension; *DM*, diabetes mellitus; *CCRT*, concurrent chemoradiotherapy; *IP*, irinotecan/platinum; *EP*, etoposide/platinum.

Table 3. Summary of previous studies on etoposide/cisplatin- or irinotecan/cisplatin-based concurrent chemoradiotherapy for limited-disease small-cell lung cancer

Author	Phase	No. of patients	Regimen	Radiation dose	RR (%)	PFS (m), <i>P</i> -value	OS (m), <i>P</i> -value	Grade 3/4 toxicity (%)
Faivre-Finn [4] (2017)	III	247	EP-CCRT BID vs. QD	45 Gy vs. 66 Gy		15.4 vs. 13.4; HR=1.12 p=0.26	30 vs. 25; HR=1.18, p=0.14; 2 year SR (56% vs. 51%)	Neutropenia (74% vs. 65%) Esophagitis (19% vs. 19%) Radiation pneumonitis (3% vs. 2%)
Kubota [12] (2014)	III	281	EP-CCRT BID followed by IP vs. EP	45 Gy		12 vs. 13.2; HR 1.10 p=0.74	33.6 vs. 38.4; HR=1.09, p=0.70; 5-year SR (33.7% vs. 35.8%)	Neutropenia (95% vs. 78%) Anemia (35% vs. 50%) Diarrhea (2% vs. 1%)
Fukuda [11] (2012)	II	34	IP-CCRT	50 Gy	100	14.3 1-, 5- year SR (56.9%, 30.2%)	44.5; 2- and 5- year SR (66.7%, 46.1%)	Neutropenia 38% Pneumonitis 6% Diarrhea 3% Esophagitis 0%
Naidu [10] (2014)	II	36	IP-CCRT BID	45-54 Gy	67		19; 1-, 2-, 3- year SR (60%, 44%, 30%)	Symptomatic pneumonitis 0% Symptomatic esophagitis 13%
Saito [14] (2006)	II	51	EP-CCRT BID followed by IP	45 Gy	88	11.8	23; 2- and 3- year SR (49%, 29.7%)	Neutropenia 88% Infection 33% Electrolyte imbalance 20% Diarrhea 14%
Jeong [23] (2006)	II	20	IP-CCRT	50.4 Gy	85	12 1-year SR 36%	20; 1- and 2- year SR (85%, 35%)	Neutropenia 60% Anemia (20%) Nausea/vomiting (55%) Diarrhea (35%)
Hong [13] (2011)	II	19	IP-CCRT QD	54 Gy	89.5	7.6	12.4; 2-year SR (75.0%)	Radiation- induced pneumonitis 53% Neutropenia 32%

Sohn [8] (2007)	II	33	IP-CCRT BID	45-54 Gy	87.9	14.4 2-year SR 26.8%	26.1; 2-year SR (54.9%)	Neutropenia 81.8% Diarrhea 21.2% Radiation pneumonitis 9.1%
Han [15] (2005)	II	33	IP followed by EP- CCRT BID	45 Gy	97	12.9 2-year SR 36.1%,	25; 1- and 2- year SR (85.7%, 53.9%)	Neutropenia (68% + 100%) ^a , Febrile neutropenia (20% + 60%) ^b

RR response rate; *PFS* progression-free survival; *OS* overall survival; *EP* etoposide/platinum; *IP* irinotecan/platinum; *CCRT* concurrent chemoradiotherapy; *BID* bis in die (twice a day); *QD* quaque die (once a day); *HR* hazard ratio; *SR* survival rate.

^aGrade 3 or 4 neutropenia occurred during induction chemotherapy in 68% patients and during CCRT in 100% patients.

^bGrade 3 or 4 febrile neutropenia occurred during induction chemotherapy in 20% patients and during CCRT in 60% patients.

Figures

Figure 1

Data mining process for identification of patients with LD-SCLC. SCLC, small-cell lung cancer; CCRT, concurrent chemoradiotherapy; LD, limited-disease; ED, extensive-disease

Figure 2

Kaplan–Meier curves for progression-free survival (PFS) (A) and overall survival (OS) (B) in patients who received an etoposide/platinum (EP)- or irinotecan/platinum (IP)-based concurrent chemoradiotherapy regimen as definite treatment for limited-disease small-cell lung cancer. CI, confidence interval

Figure 3

(A) Kaplan–Meier curves for overall survival (OS) in patients with limited-disease (LD) small-cell lung cancer (SCLC) who received combination chemotherapy (combi) or monotherapy (mono) as second-line treatment. (B) Kaplan–Meier curve for OS in patients with LD-SCLC who received the irinotecan/platinum (IP) or etoposide/platinum (EP) combination as second-line treatment. CI, confidence interval

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