석 사 학 위 논 문

# Dose Modification of Etoposide plus Platinum in Elderly Patients with Extensive-Disease Small-Cell Lung Cancer

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이 논문을 석사학위 논문으로 제출함

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계명대학교 대학원

의학과 내과학 전공

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# 최이현의 석사학위 논문을 인준함

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# 1. Introduction

Small-cell lung cancer (SCLC) comprises approximately 15%-20% of lung cancers, and about two-thirds present as an extensive disease because of a rapid doubling time (1). Extensive-disease small-cell lung cancer (ED-SCLC) is highly sensitive to an initial platinum-based chemotherapy. However, the response is seen only for a short period, and most patients experience early disease progression and death (2). For the past four decades, an etoposide plus platinum regimen has been recommended as first-line chemotherapy for ED-SCLC with a median overall survival (OS) of 9.5 months (3-5). Recently, immune checkpoint inhibitors (ICIs) have been approved as first-line combination chemotherapy with etoposide plus platinum for ED-SCLC, extending the median OS to 12.3 months (6, 7).

Most patients with ED-SCLC are older than 65 years of age (1). With an increase in life expectancy, a corresponding increase was seen in the proportion of elderly patients with SCLC; from 23% in 1975 to 44% in 2010 (8). Elderly patients have multiple comorbidities and are easily prone to face serious treatment-related toxicities. However, there is limited data on elderly patients since most trials tend to enroll young and healthy patients, and the available guidelines are based on such trials. Hence, a need for a comprehensive geriatric approach on tailored chemotherapy in elderly patients with SCLC is increasingly warranted. In addition, elderly patients with ED-SCLC sometimes refuse potentially beneficial chemotherapy because of the fear of toxicity and uncertainty (9). Physicians hesitate to treat elderly patients because of decreased organ function and often encounter early treatment-related mortality. Therefore, it is necessary to find a safe and effective method for

treating these patients.

Several studies have evaluated the prognostic factors and effects of treatment in elderly patients with SCLC. Schild et al. (10) reported that patients with SCLC over 80 years had significant survival differences with stage, performance status, and treatment options and appeared to benefit from multimodality therapy. Medical oncologists sometimes modify chemotherapy doses in high-risk elderly patients to reduce toxicity. However, there is limited data on the effect of dose-reduced chemotherapy on the survival of these elderly patients.

Therefore, this study aimed to evaluate the survival outcomes following reduced dose of first-line chemotherapy in elderly patients with ED-SCLC.

# 2. Materials and Methods

## 2.1. Study populations and methods:

We retrospectively analyzed 100 patients with ED-SCLC who were treated at Keimyung University Dongsan Hospital between January 2006 and December 2020. Patients pathologically confirmed as having SCLC according to the World Health Organization classification and only those diagnosed at the age of 70 years or above were considered for the study. Additionally, all included patients had received etoposide/cisplatin or etoposide/carboplatin every three weeks as first-line chemotherapy. Medical records were reviewed for the following characteristics: age, sex, body mass index (BMI), Eastern Cooperative Oncology Group Performance Score (ECOG PS), smoking history, date of diagnosis, disease progression, last follow-up visit, death, underlying disease, metastatic sites, and chemotherapy history including regimen, dose, cycles, and date. Smoking status included former and current smokers. We reviewed the underlying diseases: chronic lung disease (chronic obstructive pulmonary disease, interstitial lung disease, bronchiectasis), heart disease (ischemic heart disease, heart failure, arrhythmia), chronic kidney disease (CKD), chronic liver disease (viral hepatitis, liver cirrhosis), diabetes mellitus (DM), and cerebrovascular disease (CVA). Patients were divided into two groups according to whether chemotherapy was initiated with a reduced dose in the first cycle. The rate of dose reduction varied from 15% to 30%. Dose modification, including the rate of dose reduction and patient selection, depended upon clinician decision making according to the comorbidity and performance

status. Data were collected until January 15, 2021. This study was approved by the Institutional Review Board of Keimyung University Dongsan Hospital, and the requirement for written informed consent was waived owing to the retrospective nature of the study (DSMC 2021-09-013).

## 2.2. Statistical analyses:

The distribution of variables between groups was assessed using Student's t-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. The intervals between the time from the start date of chemotherapy to disease progression or death were calculated for each patient. Overall survival (OS) and progression-free survival (PFS) were evaluated using the Kaplan-Meier method and groups were compared by applying the log-rank test. A multivariate Cox proportional hazards regression model was used to evaluate the prognostic factors for OS in elderly patients with ED-SCLC. The results are presented as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Statistical significance was set at $p < 0.05$. All analysis was performed using IBM SPSS Statistics for Windows (version 25.0; IBM Corp., Armonk, NY, USA).

# 3. Results

## 3.1. Patients' characteristics:

The characteristics of the 100 patients included in the study are shown in Table 1. The median age was 74 years (range, 70-85 years), and majority were males (84.0%). The median BMI was 21.7 kg/m$^2$ (range, 15.2-30.4 kg/m$^2$), and 72 patients (72%) had an ECOG PS of 0-2. Eighty-nine patients (89%) had a history of smoking. The underlying conditions included lung disease (38%), cardiovascular disease (21%), renal disease (7%), liver disease (6%), DM (28%), and CVA (16%). Among the patients, 19%, 30% and 44% had brain, liver, and bone metastases, respectively. Most patients received an etoposide plus cisplatin regimen (83%), and the median number of cycles of chemotherapy was four (range, 1-6). Sixty-four patients (64%) experienced a dose reduction during chemotherapy. At the time of cut-off, death occurred in 95 (95%). The median OS and PFS of all patients were 6.3 (95% CI 4.535-8.065) and 4.5 months (95% CI 3.791-5.209), respectively.

## 3.2. Effect of dose-reduced chemotherapy on survival outcomes in elderly ED SCLC patients:

We evaluated the effect of dose-reduced chemotherapy on survival outcomes in elderly patients with ED-SCLC. The characteristics and

comparisons between the two groups are presented in Table 1. Of the 100 patients, 34 (34%) received dose-reduced etoposide plus platinum chemotherapy from the first cycle. The dose-reduced group had significantly higher age, lower BMI, and poor ECOG PS than the other group.

The median OS and PFS of patients with dose-reduced chemotherapy were 4.9 months (95% CI 0.000-10.471) and 3.7 months (95% CI 2.673-4.727), and respectively. The median OS and PFS of patients who received full-dose chemotherapy were 6.5 (95% CI 4.666-8.334) and 4.6 months (95% CI 3.924-5.276), respectively. However, there were no significant differences in survival outcomes between the two groups (median OS, 4.9 vs. 6.5 months, $p = 0.440$; median PFS, 3.7 vs. 4.6 months, $p = 0.272$; Figure 1A, B). Following multivariate analyses, it was seen that ECOG PS 3-4 (HR 4.992, 95% CI 2.640-9.437; $p < 0.001$), smoking (HR 2.988, 95% CI 1.215-7.438; $p = 0.017$), lung disease (HR 1.690, 95% CI 1.005-2.841; $p = 0.048$), brain metastasis (HR 2.685, 95% CI 1.383-5.215; $p = 0.004$), liver metastasis (HR 2.042, 95% CI 1.201-3.472; $p = 0.008$), and dose reduction in the first cycle (HR 0.519, 95% CI 0.269-1.000, $p = 0.050$) were significantly associated with OS (Table 2).

## 3.3. Subgroup analysis of patients receiving no less than four cycles of first-line chemotherapy:

Many patients had to discontinue chemotherapy in the early cycles for several reasons, including toxicity. To compare the efficacy of

dose-reduced chemotherapy, we conducted a subgroup analysis of patients who received minimum four cycles of the first-line chemotherapy. In all, 59 (59%) received four or more cycles. The median OS and PFS of patients who received dose-reduced chemotherapy were 10.9 (95% CI 6.326-15.474) and 6.3 months (95% CI 5.053-7.547), respectively. The median OS and PFS of patients who received full-dose chemotherapy were 9.4 (95% CI 7.088-11.712) and 6.5 months (95% CI 5.666-7.334), respectively. There were no significant differences in survival outcomes between the dose-reduced and full-dose chemotherapy (median OS, 10.9 vs. 9.4 months, p = 0.817; median PFS, 6.3 vs. 6.5 months, p = 0.902; Figure 2A, B). We reviewed the cause of fewer than four cycles of chemotherapy in 41 patients. Disease progression was noted in only seven patients (17.1%) and 19 patients died (46.3%). Fifteen patients (36.6%) stopped chemotherapy due to the decreased performance status (Table 3).

Table 1. Characteristics of Elderly Patients with Extensive-Stage Small Cell Lung Cancer According to Dose Reduction

| Characteristics | | Total (n = 100) | DR** at 1st cycle | | |
|---|---|---|---|---|---|
| | | | Yes (n = 34) | No (n = 66) | *p* |
| Age (years) | | 74 (70-85) | 78.5 (70-85) | 74 (70-85) | 0.000 |
| Sex | Male | 84 (84.0) | 26 (76.5) | 58 (87.9) | 0.140 |
| | Female | 16 (16) | 8 (23.5) | 8 (12.1) | |
| BMI* ($kg/m^2$) | | 21.7 (15.2-30.4) | 20.7 (16.2-30.0) | 22.8 (15.2-30.4) | 0.012 |
| ECOG PS§ | 0 - 2 | 72 (72.0) | 20 (58.8) | 54 (78.8) | 0.035 |
| | 3 - 4 | 28 (28.0) | 14 (41.2) | 14 (21.2) | |
| Smoker | Yes | 89 (89.0) | 31 (91.2) | 58 (87.9) | 0.745 |
| | No | 11 (11.0) | 3 (8.8) | 8 (12.1) | |
| Lung disease | Yes | 38 (38.0) | 16 (47.1) | 22 (33.3) | 0.180 |
| | No | 62 (62.0) | 18 (52.9) | 44 (66.7) | |
| Heart disease | Yes | 21 (21.0) | 6 (17.6) | 15 (22.7) | 0.555 |
| | No | 79 (79.0) | 28 (82.4) | 51 (77.3) | |
| Renal disease | Yes | 7 (7.0) | 3 (8.8) | 4 (6.1) | 0.687 |
| | No | 93 (93.0) | 31 (91.2) | 62 (93.9) | |
| Liver disease | Yes | 6 (6.0) | 0 (0.0) | 6 (9.1) | 0.093 |
| | No | 94 (94.0) | 34 (100.0) | 60 (90.9) | |
| Diabetes mellitus | Yes | 28 (28.0) | 8 (23.5) | 20 (30.3) | 0.475 |
| | No | 72 (72.0) | 26 (76.5) | 46 (69.7) | |
| Crebrovascular disease | Yes | 16 (16.0) | 4 (11.8) | 12 (18.2) | 0.407 |
| | No | 84 (84.0) | 30 (88.2) | 54 (81.8) | |
| Brain metastasis | Yes | 19 (19.0) | 9 (26.5) | 10 (15.2) | 0.172 |
| | No | 81 (81.0) | 25 (73.5) | 56 (84.8) | |
| Liver metastasis | Yes | 30 (30.0) | 9 (26.5) | 21 (31.8) | 0.580 |
| | No | 70 (70.0) | 25 (73.5) | 45 (68.2) | |
| Bone metastasis | Yes | 44 (44.0) | 14 (41.2) | 30 (45.5) | 0.683 |
| | No | 56 (56.0) | 20 (58.8) | 36 (54.5) | |
| Regimen | EP*** | 83 (83.0) | 26 (76.5) | 57 (86.4) | 0.212 |
| | EC‖ | 17 (17.0) | 8 (23.5) | 9 (13.6) | 0.741 |
| Total cycles | | 4 (1-6) | 4 (1-6) | 4 (1-6) | |
| DR at any cycle | Yes | 64 (64.0) | 34 (100.0) | 36 (54.5) | 0.000 |
| | No | 36 (36.0) | 0 (0.0) | 30 (45.5) | |

* BMI, body mass index; ** DR, dose reduction; *** EC, etoposide/carboplatin; § ECOG PS, Eastern Cooperative Oncology Group performance score; ‖, EP, etoposide/cisplatin.

Table 2. Cox Regression Multivariate Analyses of Factors for Overall Survival in Elderly Patients with Extensive-Stage Small Cell Lung Cancer

| Multivariate analysis | HR§ (95% CI) | *p* |
|---|---|---|
| Female vs. Male | 2.028 (0.886-4.644) | 0.094 |
| ECOG PS** | 4.992 (2.640-9.437) | 0.000 |
| Smoker | 2.988 (1.215-7.438) | 0.017 |
| Lung disease | 1.690 (1.005-2.841) | 0.048 |
| Heart disease | 1.242 (0.718-2.148) | 0.438 |
| Renal disease | 0.673 (0.268-1.689) | 0.399 |
| Liver disease | 0.814 (0.309-2.146) | 0.677 |
| Diabetes mellitus | 0.827 (0.491-1.393) | 0.474 |
| Cerebrovascular disease | 0.683(0.336-1.389) | 0.293 |
| Brain metastasis | 2.685 (1.383-5.215) | 0.004 |
| Liver metastasis | 2.042 (1.201-3.472) | 0.008 |
| Bone metastasis | 1.431 (0.874-2.343) | 0.154 |
| Regimen, EC* vs. EP*** | 0.896 (0.451-1.781) | 0.755 |
| Dose reduction at 1$^{st}$ cycle | 0.519 (0.269-1.000) | 0.050 |
| Dose reduction at any cycle | 1.398 (0.795-2.456) | 0.245 |

* EC, etoposide/carboplatin; ** ECOG PS, Eastern Cooperative Oncology Group performance score; *** EP, etoposide/cisplatin; § HR, hazard ratio.

Table 3. Causes for Less than Four Cycles of the First-Line Chemotherapy in Elderly Patients with Extensive-Stage Small Cell Lung Cancer

| Cause | Total (n = 41) |
|---|---|
| Death | 19 |
| Decreased performance status | 15 |
| Disease progression | 7 |

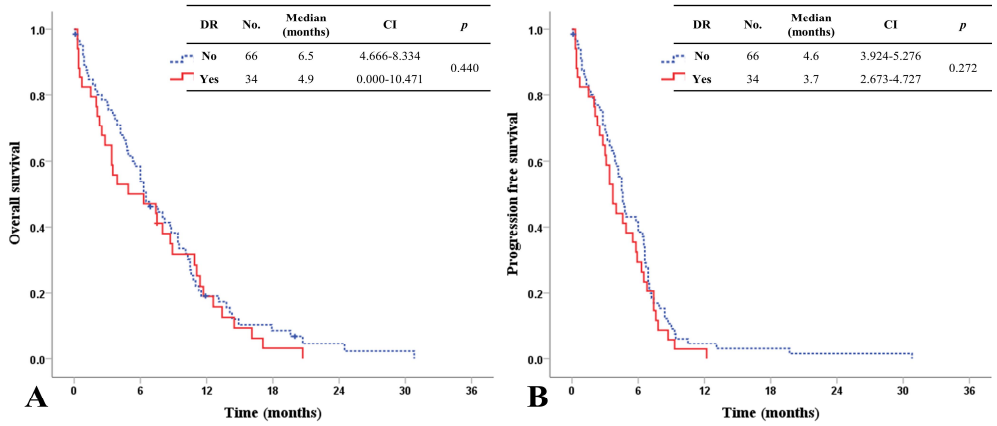


Figure 1. Overall survival (A) and progression free survival (B) in elderly patients with extensive-stage small cell lung cancer according to dose reduction.

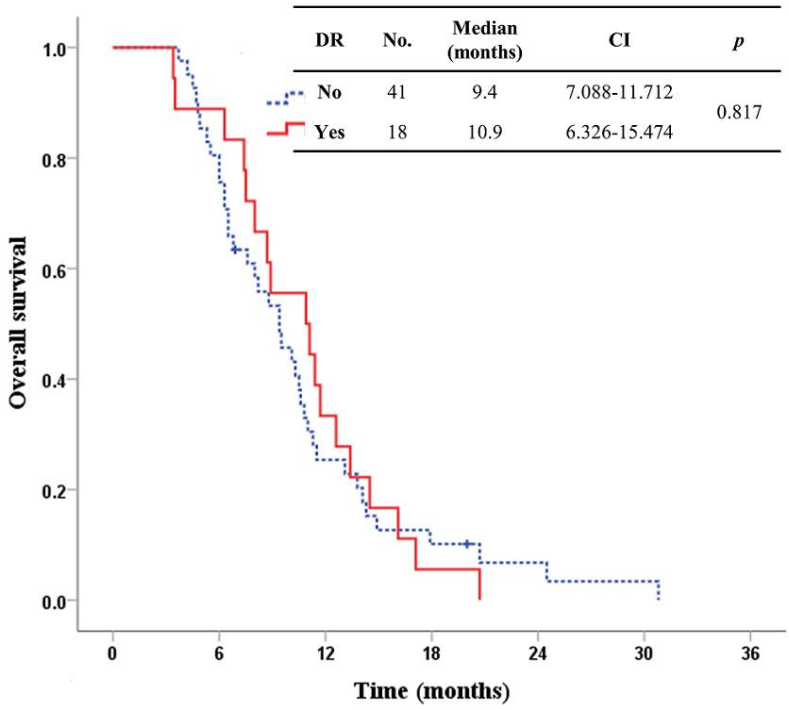


Figure 2. Overall survival in elderly extensive-stage small cell lung cancer patients received no less than four cycles of the first-line chemotherapy according to dose reduction.

# 4. Discussion

Elderly patients with ED-SCLC are difficult to treat with chemotherapy because of multiple comorbidities and poor performance status. Though, a dose reduction is often considered to decrease chemotherapy associated toxicity, there is no evidence to show how much this strategy affects the survival outcomes. In the present study, we compared the dose-reduced and full-dose first-line chemotherapy in elderly patients with ED-SCLC. We found no significant differences in OS and PFS between the groups, although the dose-reduced group had higher age, lower BMI, and poor ECOG PS. Furthermore, following multivariate analyses, it was seen that survival significantly improved in patients in the dose-reduced chemotherapy group.

With increase in the geriatric population, the incidence of cancer is expected to increase. Several studies have been conducted to reduce chemotherapy toxicity in the elderly, including the use of granulocyte colony-stimulating factor (11, 12) and the modification of treatment regimens (13). Kotsori et al. (14) analyzed palliative capecitabine monotherapy in 89 elderly patients with locally advanced or metastatic breast cancer, including 34 patients (41%) with a 25% dose reduction at the start. The study revealed that there was no significant difference in efficacy between the full and reduced doses. In elderly patients with ED-SCLC, etoposide plus carboplatin can be an alternative to etoposide plus cisplatin since it has been reported that this approach does not significantly affect the response rate (73% vs. 73%) and overall survival (median 10.6 vs. 9.9 months, p = 0.54) (4). In addition, Hatfield et al. demonstrated that etoposide plus carboplatin is a better option because of the similar efficacy with reduction in the post-treatment utilization of

hospital-based health care (15). Concerns about vulnerability of elderly patients may make it difficult to decide whether or not to administer chemotherapy. The possible impact of dose-reduced chemotherapy on unfavorable prognoses adds to this (16). The limitations of our knowledge provided the rationale for conducting this study to compare the dose-reduced versus full-dose chemotherapy in elderly patients with ED-SCLC.

We demonstrated no statistically significant difference in OS and PFS between the two groups. However, it did show a numerically lower survival duration in the dose-reduced group. Inevitably, the dose-reduced group had high-risk patients in terms of age, BMI, and performance. Hence, almost 50% of patients in the dose-reduced group did not complete four cycles, and half of the remaining completed only one cycle. To compare the efficacy of chemotherapy, we conducted a subgroup analysis of patients who completed four cycles. Contrary to available reports, in this study, though there were no significant differences between the two groups, a numerical improvement in OS was noted in the dose-reduced group. Among 41 patients who failed to finish four cycles, 37% gave up treatment due to decreased performance status without proof of disease progression. These results suggest that it is important to assess a feasible approach for elderly patients to safely undergo four or more cycles of chemotherapy. Toward this, an initial dose reduction seems to be an appropriate solution without a negative effect on the survival outcome.

ICIs have gained a paradigm shift in cancer treatment. In 2019, based on IMpower133 (6, 7) and CASPIAN trials (17, 18), the Food and Drug Administration approved atezolizumab or durvalumab combined chemotherapy as first-line treatment in ED-SCLC patients. This introduction has changed the standard of care and extended the OS of

ED-SCLC patients to more than one year. It is a welcome relief because there has been no progress in treatment and survival outcomes of these patients over the past 20 years. For elderly patients with ED-SCLC, ICI offers a breakthrough therapeutic option with a relatively favorable toxicity profile (10). Notably, according to the findings of the IMpower 133 trial, the benefit of atezolizumab was higher in elderly patients (< 65 years, HR 0.92, 95% CI 0.64-1.32; ≧ 65 years, HR 0.53, 95% CI 0.36-0.77). Unfortunately, in the present study, we had to exclude a small number of patients who underwent ICI from the analysis of unified groups since only patients diagnosed between 2006 and 2020 were enrolled. It is envisaged that ICI plus dose-reduced chemotherapy may lead to better survival outcomes beyond non-inferiority. Therefore, further studies to verify the effect of ICI plus dose-reduced chemotherapy in elderly patients in the era of immunotherapy are warranted.

This study has several limitations. First, as this was a retrospective study, the confounding factors could not be controlled. Non-random distribution could cause selection bias leading to differences between groups. Second, the relatively small sample size of this study may have undermined the reliability of the findings. Third, we defined elderly patients as ≧ 70 years of age in this study, which is the same criterion as many previously reported studies. However, due to lack of consensus on the age-related definition, this may be controversial. Fourth, the rate of dose reduction was at the physicians' discretion, and the reduction was not uniform and varied from 15% to 30%. In addition, this analysis did not include a comprehensive geriatric assessment since it was not routinely performed. Overall, these results need to be verified in a large-scale prospective study. Nevertheless, this study does give meaningful insights in this field and suggests directions for future

research in geriatric oncology.

This study showed that dose-reduced chemotherapy with first-line etoposide plus platinum had non-inferior survival outcomes compared to full-dose chemotherapy in elderly patients with ED-SCLC. These findings further suggest that geriatric assessments that are effective in elderly patients with ED-SCLC need to be developed toward selection of an optimal candidate. For future progress studies that focus on combination immunotherapy in the elderly are needed.

# 5. Summary

In elderly patients with ED-SCLC, dose-reduced chemotherapy with first-line etoposide and platinum showed non-inferior survival outcomes compared to full-dose chemotherapy. These findings further suggest that geriatric assessments that are effective in elderly patients with ED-SCLC need to be developed toward selection of an optimal candidate. Future progress requires studies focusing on complex immunotherapy in the elderly.

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randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2021;22:51-65.

# Dose Modification of Etoposide plus Platinum in Elderly Patients with Extensive-Disease Small-Cell Lung Cancer

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(Supervised by Professor Park, Keon Uk)

(Abstract)

Purpose: Elderly patients with extensive-disease small-cell lung cancer (ED-SCLC) have a high risk of chemotherapy toxicity due to multiple comorbidities and poor performance status. Although dose modification is often used to avoid toxicity in elderly patients with ED-SCLC, there is little data on the effect of initial dose-reduced chemotherapy on survival outcomes.

Materials and Methods: We retrospectively reviewed 100 elderly patients with ED-SCLC who received first-line etoposide plus platinum chemotherapy between January 2006 and December 2020.

Results: The median age was 74 years. Eighty-nine patients (89%) had

a history of smoking, and 38 (38%) had chronic lung disease. Thirty-four patients (34%) received dose-reduced etoposide plus platinum in the first cycle. The dose-reduced group had significantly higher age, lower body mass index, and poor Eastern Cooperative Oncology Group performance score. There were no significant differences in survival outcomes between the dose-reduced and full-dose chemotherapy [median overall survival (OS), 4.9 vs. 6.5 months, p = 0.440; median progression free survival (PFS), 3.7 vs. 4.6 months, p = 0.272]. In multivariate analyses, dose reduction in the first cycle (hazard ratio 0.519, 95% CI 0.269-1.000, p = 0.050) was significantly associated with OS. Following subgroup analysis of 59 patients who received minimum four cycles, no significant differences in survival outcomes between the two groups (median OS, 10.9 vs. 9.4 months, p = 0.817; median PFS, 6.3 vs. 6.5 months, p = 0.902) was noted.

Conclusion: The dose-reduced chemotherapy with first-line etoposide plus platinum had non-inferior survival outcomes compared to the full-dose chemotherapy in elderly patients with ED-SCLC.

# 고령의 확장기 소세포폐암 환자에서 Etoposide와 Platinum의 용량 조절

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목적: 고령의 확장기 소세포폐암 환자는 복합적 동반 질환과 낮은 수행 능력 상태로 인해 화학요법 독성의 위험이 높다. 확장기 소세포폐암이 있는 고령 환자에서 독성을 피하기 위해 용량 조절이 종종 사용되지만 초기 용량 감소 화학요법이 생존 결과에 미치는 영향에 대한 데이터는 거의 없다.

재료 및 방법: 2006년 1월부터 2020년 12월 사이에 1차 Etoposide와 백금 화학요법을 받은 확장기 소세포폐암 노인 환자 100명을 후향적으로 검토했다.

결과: 중앙값은 74세였다. 89명의 환자(89%)는 흡연력이 있었고 38명(38%)은 만성 폐질환이 있었다. 34명의 환자(34%)가 첫 번째 주기에서 용량 감소 된 Etoposide와 백금을 투여받았다. 용량 감소 그룹은 유의하게 더 높은 연령, 더 낮은 체질량 지수 및 낮은 수행 능력 상태를 보였다. 용량 감소 및 전체 용량 화학요법 간의 생존 결과에는 유의한 차이가 없었다

[전체 생존 중앙값, 4.9 대 6.5개월, p = 0.440; 무진행 생존 중앙값, 3.7 대 4.6개월, p = 0.272]. 다변수 분석에서 첫 번째 주기의 용량 감소 (위험비 0.519, 95% CI 0.269-1.000, p = 0.050)는 전체 생존과 유의하게 관련이 있었다. 최소 4주기를 받은 59명의 환자에 대한 하위 그룹 분석 결과, 두 그룹 사이의 생존 결과에 유의미한 차이가 없었다(전체 생존 중앙값, 10.9 대 9.4 개월, p = 0.817; 무진행 생존 중앙값, 6.3 대 6.5 개월, p = 0.902).

결론: 1차 Etoposide와 백금을 사용한 용량 감소 화학요법은 확장기 소세포폐암이 있는 고령 환자에서 전체 용량 화학요법에 비해 비열등한 생존 결과를 보였다.