Comparison of the efficacy of cisplatin and carboplatin in combination with etoposide in firstline treatment of extensive-stage small cell lung cancer in real-world practice in the Czech Republic – a retrospective analysis of patients from the LUCAS project

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Background. Patients with extensive-stage small-cell lung cancer (ES-SCLC) have a poor prognosis. The standard palliative treatment for four decades has been chemotherapy as a combination of etoposide with carboplatin or cisplatin, and in recent years, immunotherapy in addition.
Aims. To determine whether there is a difference in the efficacy of palliative chemotherapy as cisplatin or carboplatin in combination with etoposide in patients with ES-SCLC in real-world practice in the Czech Republic.
Methods. This was a retrospective analysis of a cohort of 348 patients from the LUCAS project with ES-SCLC. 79 were treated with etoposide plus cisplatin and 265 were treated with etoposide plus carboplatin. Kaplan-Meier curves and the Cox regression model were used for analysis.
Results. No statistically significant difference in median overall survival (mOS) or median progression free survival (mPFS) was found between groups or between patients grouped according to age and performance status (PS) in mOS. The Cox regression result was similar.
Conclusion. This study shows that cisplatin and carboplatin do not differ in efficacy in a given indication, thus when choosing a treatment, the physician should consider the expected toxicity in a particular patient, assessing the patient's general condition and comorbidities.

Key words: small cell lung cancer, extensive-stage, carboplatin, cisplatin

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INTRODUCTION

Lung cancer is one of the most common cancers and has a poor prognosis. In 2018, the incidence of this disease in the Czech Republic was 60.8 per 100,000 persons and the mortality rate was 49.6 per 100,000 persons[1]. Small cell lung cancer (SCLC) was present in 14% of all reported lung cancers in the country between 2014 and 2018 and accounted for 17.7% of those lung cancers in which histology was determined[1]. SCLC is more strongly associated with smoking than other histological types of lung cancer, occurring almost exclusively in smokers. The rare occurrence of this disease in non-smokers is associated with older age and exposure to radon[2,3].

Currently, the 8th edition of the TNM classification according to the IASLC (International Association for the Study of Lung Cancer) is used for staging SCLC, and the Veteran's Administration Lung Cancer Study Group's division into extensive (ES-SCLC) and limited disease (LS-SCLC) is used concurrently. At the time of diagnosis of SCLC, approximately 60% of cases are in the ES-SCLC stage[4]. Currently used treatment of ES-SCLC is only palliative, alleviating disease symptoms, improving quality of life and significantly prolonging patient survival.

The median overall survival (mOS) of ES-SCLC patients treated with first-line chemotherapy alone ranges between 9 and 13 months[5-7], and little progress has been made in treating these patients over the past 40 years.

Before the introduction of platinum derivatives, the chemotherapeutic combination of CAV (cyclophosphamide, doxorubicin, vincristine) was the drug of choice for SCLC. Since the 1980s, etoposide with a platinum derivative (carboplatin or cisplatin) has been the drug of choice for four decades[8].

Although other chemotherapy drugs and different regimens were tested, no significant advances in treatment were made for a long time. The hope for more prolonged survival of these patients has only recently come with the introduction of immunotherapy in combination with chemotherapy. After a long time, a new treatment regimen has emerged with proven survival prolongation based on the phase III randomized trials IMPOWER133 and CASPIAN (ref.[9,10]). Although immunotherapy has clinical benefit for some patients and can bring long-term survival for them, the improvement in mOS for ES-SCLC patients altogether only reaches two to three months.

For patients who achieved response after chemotherapy, thoracic radiotherapy can prolong survival[11].

The introduction of screening is not expected to improve the outcome of the patients. Screening for lung cancer with low-dose computed tomography for high-risk patients has been shown to reduce mortality from non-small cell lung cancer in international studies, but SCLC patients have not benefited from this programme[12]. This is probably due to the aggressiveness of the disease, for which a one-year interval between examinations allows sufficient time for symptomatic disease to develop.

Thus, the standard of care for SCLC remains a chemotherapeutic doublet with a platinum derivative, either in combination with radiotherapy for limited stage or in combination with immunotherapy for extensive stage, with no clear criteria for the clinician to choose between carboplatin and cisplatin in combination with etoposide. The two platinum derivatives differ in the spectrum of adverse effects and efficacy depending on the indication. For some types of tumours, such as ovarian cancer, carboplatin is recommended as a more effective choice than cisplatin according to randomized trials, whereas cisplatin is considered more effective in other indications[13,15]. In the case of lung cancer, it is not entirely clear in which cases carboplatin is preferable to cisplatin. Carboplatin is currently preferred as palliative therapy for ES-SCLC in Czech Republic, mainly because of its lower toxicity[16]. The decision between these options is always up to the physician after taking into account the clinical condition of the patient, his/her comorbidities and the expected efficacy and toxicity of the treatment.

This study aimed to compare the treatment of patients with ES-SCLC from real-world practice in the Czech Republic and whether survival differs depending on the chemotherapeutic regimen used: etoposide plus cisplatin versus etoposide plus carboplatin.

METHODS

Lucas project

The LUCAS (Lung Cancer Focus) project is a non-interventional, lifetime follow-up of patients with newly diagnosed lung cancer from the time of diagnosis. It has been operating in the Czech Republic since 1 June 2018 and collects comprehensive data on the diagnosis and treatment of these patients. Eleven hospital centres are currently collaborating on the project. The LUCAS is a joint project of the Czech Pneumological and Phthisiological Society, Czech Medical Association of J. E. Purkyně and the OAKS Consulting s.r.o., which is responsible for project management and processing outputs. The project is registered on ClinicalTrials.gov under registration number NCT04228237. All participants were required to sign an informed consent form, which had been approved by the Ethics Committee, as a prerequisite to their participation in the project.

In the LUCAS project, basic demographic and clinical characteristics, performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG), morphological, immunohistochemical, immunochemical and molecular genetic characteristics, data about pharmacotherapy (including types, combinations and sequences), data about the interventions (including surgery, radiotherapy etc.) are recorded.

Study population

At the time of export (as of November 30, 2022), 877 patients with SCLC (all stages of disease) were in the LUCAS project. Patients who were concurrently enrolled in another clinical trial (4), patients who were lost to follow-up before diagnosis (3), and those who had a diagnosis after the identification date of March 31, 2022 (70) were excluded from the analysis. In addition, 205 patients who have not been treated in the pneumooncology centres, which are part of the LUCAS project, were excluded. Moreover, 30 patients whose treatment included chemotherapy other than the combination of etoposide and a platinum derivative were excluded.

From the remaining 565 patients, patients fulfilling the ES-SCLC criteria were selected – patients with a staging of any T, any N and any M1, and those for whom no curative radiotherapy combined with chemotherapy was indicated in the project.

Thus, 348 patients who met all entry criteria were included in the survival analysis. Of these 348 patients, four patients who were treated with both cisplatin and carboplatin combinations were excluded from OS and progression-free survival (PFS) analyses (Fig. 1).

Statistical analysis

Survival analysis methods, including Kaplan-Meier curves, were used to analyse the time to death of patients. The date of death was obtained from the Czech Statistical Office as of 31 March 2022. These data were supplemented with death information from "Reimbursement payment (K-batch)" and from the CLADE information

system for manual data entry into the LUCAS project. Living patients were censored at the last date they were known to be alive. Moreover, two patients were censored at the date of loss to follow-up. For the analysis of PFS, an event was defined as death or tumour progression. Basic statistics such as the proportion of patients with a recorded event, mOS with a 95% confidence interval were presented. The log-rank test (Mantel-Cox) and Cox regression model were used to compare survival between the study groups. The influence of a given variable on OS is then quantified using hazard ratios (HR). The proportionality assumption was tested using the Schoenfeld's global test (P=0.71) and visually checked on a Schoenfeld residual plot. The results pointed that the proportionality assumption was not violated. For a categorical variable, for instance, patients have a 2-fold higher risk of an event at HR = 2 of a given category than patients in the reference category if the values of the other variables remain unchanged. Continuous variables were tested using the Mann-Whitney test; either the Pearson's χ^2 test or Fisher's exact test was used for categorical variables. Hypothesis testing was performed at a 5% significance level. *P*-values lower than this level correspond to statistically significant differences. The analysis was performed using IBM SPSS Statistics 29, and R software was utilized to plot the survival curves.

RESULTS

Patients characteristics, the overall survival and PFS

In the total number of 348 patients analysed, males predominated, accounting for about two-thirds of the patients. Almost all patients were smokers or ex-smokers. 76% of patients were treated with a combination of etoposide and carboplatin, less than 23% were treated with a combination of etoposide and cisplatin, and 1% of patients (four in total) received both combinations consecutively (Table 1). On average, the cisplatin-treated group had slightly younger patients and more active smokers, whereas the groups did not differ statistically significantly in gender, radiotherapy use or PS (Table 2). The total number of patients who died during the study was 280 (80.5%). We found no statistically significant difference in mOS (6.68 months for cisplatin, 7.34 months for carboplatin, *P*=0.44) or median PFS (mPFS) (5.63 months for cisplatin, 5.55 months for carboplatin, *P*=0.53) of patients treated with cisplatin compared to patients treated with carboplatin (Tables 3 and 4, Fig. 2 and 3).

Effect of age and performance status on survival

Since the known prognostic factors are mainly PS and age, we performed survival analysis, particularly for the groups with good PS (0–1) and worse PS (2–3) and particularly for the age category below 70 years and 70 years and above.

In the cohort of 344 patients, 239 patients had PS 0–1 and 88 patients had PS 2–3, 17 patients had unknown PS. Patients with good PS (0–1) had a mOS of

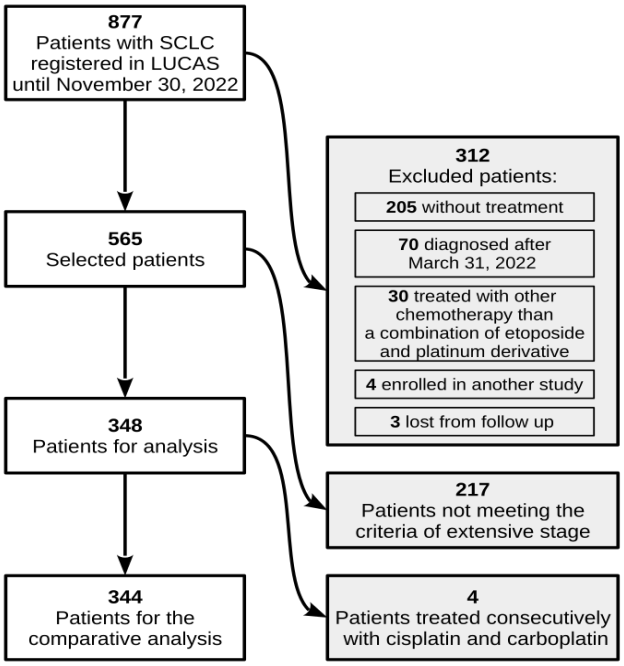

Fig. 1. Study flowchart.

Table 1. Representation of basic demographic and clinical characteristics for the study population.

Parameters	N (percentage)
Gender	
Male	227 (65.2 %)
Female	121 (34.8 %)
Age at diagnosis (years)	
Mean (SD)	69.00 ± 8.322
Median	69
Minimum–maximum	32–88
5. percentile; 95. percentile	52.00; 80.00
Smoking status	
Smoker	223 (64.1 %)
Former smoker	99 (28.4 %)
Non-smoker	15 (4.3 %)
Unknown	11 (3.2 %)
Performance status (ECOG)	
0	43 (12.4 %)
1	198 (56.9 %)
2	81 (23.3 %)
3	9 (2.6 %)
Not evaluated	17 (4.9 %)
Type of treatment	
Chemotherapy	252 (72.4 %)
Chemotherapy plus radiotherapy	96 (27.6 %)
Combination of chemotherapy	
Etoposide plus cisplatin	79 (22.7 %)
Etoposide plus carboplatin	265 (76.1 %)
Etoposide plus cisplatin plus carboplatin	4 (1.1 %)

ECOG, Eastern Cooperative Oncology Group; ICD, International Classification of Diseases; N, denominator; SD, standard deviation.

Table 2. Representation of basic demographic and clinical characteristics for the ES-SCLC study population concerning the type of chemotherapy combination used.

	Etoposide plus cisplatin N = 79	Etoposide plus Carboplatin N = 265	Total N = 344	Comparison *P**
Gender				
Male	45 (57.0%)	178 (67.2%)	223 (64.8%)	0.064
Female	34 (43.0%)	87 (32.8%)	121 (35.2%)	
Age at diagnosis (years)				
Mean (SD)	65.09 ± 9.662	69.43 ± 7.664	68.43 ± 8.354	
Median	66	70	69	
Minimum–maximum	32–85	46–88	32–88	<0.001
5. percentile; 95. percentile.	47; 80	55; 81	52; 80	
Smoking status				
Smoker	64 (81.0%)	158 (59.6%)	222 (64.5%)	
Former smoker	13 (16.5%)	83 (31.3%)	96 (27.9%)	0.006
Non-smoker	1 (1.3%)	14 (5.3%)	15 (4.4%)	
Unknown	1 (1.3%)	10 (3.8%)	11 (3.2%)	
PS (ECOG)				
0	14 (17.7%)	29 (10.9%)	43 (12.5%)	
1	49 (62.0%)	147 (55.5%)	196 (57.0%)	0.176
2	12 (15.2%)	68 (25.7%)	80 (23.3%)	
3	1 (1.3%)	7 (2.6%)	8 (2.3%)	
Not evaluated	3 (3.8%)	14 (5.3%)	17 (4.9%)	
Type of treatment				
Chemotherapy	62 (78.5%)	187 (70.6%)	249 (72.4%)	0.107
Chemotherapy plus radiotherapy	17 (21.5%)	78 (29.4%)	95 (27.6%)	

ECOG, Eastern Cooperative Oncology Group; N, denominator; SD, standard deviation
*Continuous variables were tested using Mann-Whitney test, for categorical variables using Pearson's χ^2 test or Fisher's exact test.

Table 3. Survival of patients treated with the combination of cisplatin plus etoposide or carboplatin plus etoposide.

	Cisplatin plus etoposide **(N = 79)**	Carboplatin plus etoposide **(N = 265)**
Number of censored patients	20 (25.3%)	48 (18.1%)
Number of events	59 (74.7%)	217 (81.9%)
Median OS (95% CI) (months)	6.680 (5.004–8.356)	7.340 (6.610–8.070)
Log-rank (Mantel-Cox)	*P*=0.44	

CI, confidence interval; N, denominator; OS, Overall Survival.

Table 4. Progression-free survival of patients treated with the combination of etoposide plus cisplatin or etoposide + carboplatin.

	Cisplatin plus etoposide **(N = 79)**	Carboplatin plus etoposide **(N = 265)**
Number of censored patients	17 (21.5 %)	43 (16.2 %)
Number of events	62 (78.5 %)	222 (83.8 %)
Median PFS (95% CI) (months)	5.630 (4.568–6.692)	5.590 (4.802–6.378)
Log-rank (Mantel-Cox)	*P*=0.53	

CI, confidence interval; N, denominator; PFS, progression free survival.

7.83 months (95% CI 7.16–8.50) in contrast, patients with worse PS (2–3) had a mOS of 5.00 months (95% CI 3.41–6.59), a statistically significant difference (*P*=0.001, log-rank [Mantel-Cox]) A total of 176 patients with good PS (0–1) treated with carboplatin combination had a mOS of 7.90 months (95% CI 7.15–8.65). 63 patients with good PS (0–1) treated with cisplatin had a mOS of 7.14 months (95% CI 5.43–8.85). There was no statistically significant difference in mOS between these groups (*P*=0.829, log-rank [Mantel-Cox]). 75 patients with worse PS (2–3) treated with carboplatin combination had a mOS of 5.30 months (95% CI 4.06–6.54), 13 patients with worse PS (2–3) treated with cisplatin combination had a mOS of 3.68 months (95% CI 0.00–7.41), again a not statistically significant difference (*P*=0.865, log-rank [Mantel-Cox]).

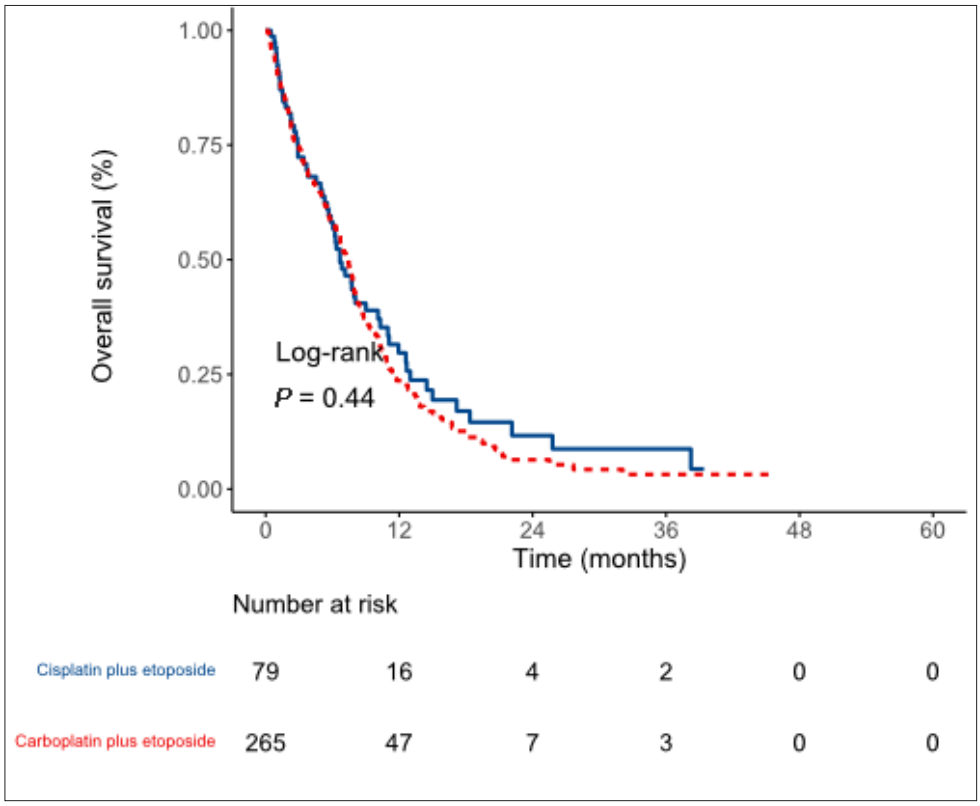

Fig. 2. Survival analysis using Kaplan-Meier curves.

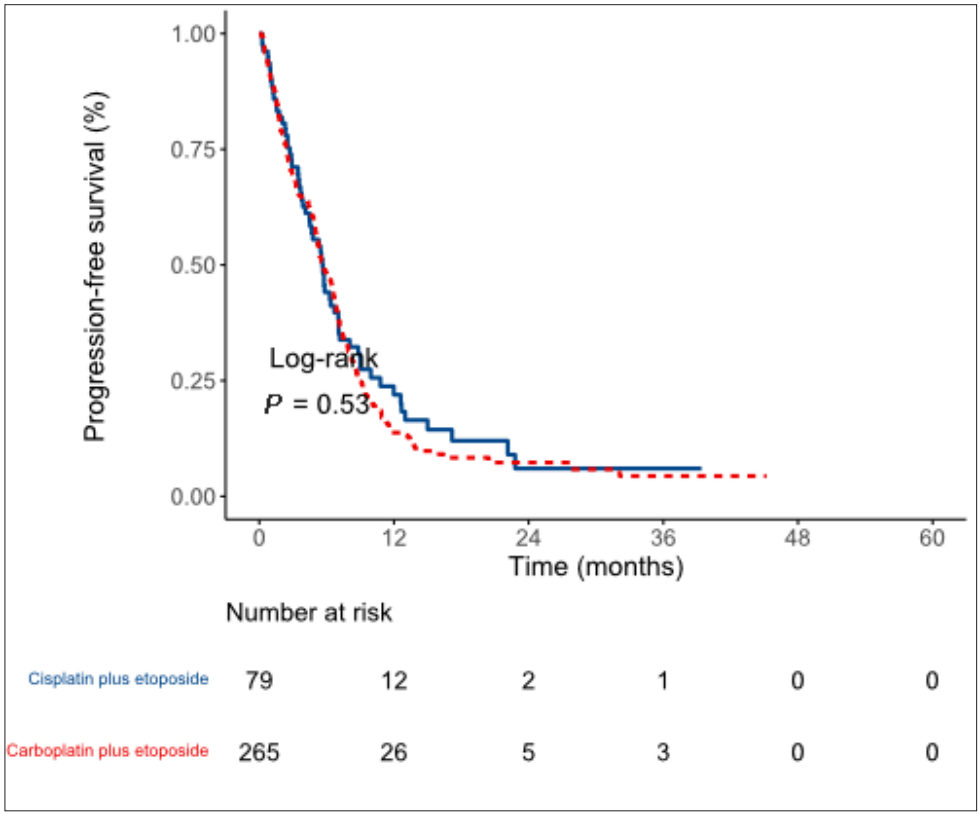

Fig. 3. Progression-free survival analysis using Kaplan-Meier curves.

Table 5. Cox regression model of overall survival.

	HR	95% CI	*P*
Performance status (ECOG)			
0	Ref.	–	–
1	1.36	0.918–2.027	0.12
2	2.07	1.325–3.228	**0.001**
3	4.11	1.797–9.416	**<0.001**
Not evaluated	1.35	0.700–2.592	0.37
Smoking status			
Non-smoker	Ref.	–	–
Smoker	1.06	0.579–1.946	0.85
Former smoker	0.78	0.417–1.458	0.44
Unknown	1.25	0.493–3.166	0.64
Gender			
Female	Ref.	–	–
Male	0.89	0.690–1.160	0.4
Age at diagnosis (years)			
<70	Ref.	–	–
≥ 70	1.41	1.087–1.823	**0.01**
Type of treatment			
Chemotherapy	Ref.	–	–
Chemotherapy plus radiotherapy	0.64	0.481–0.842	**0.002**
Combination of chemotherapy			
Etoposide plus cisplatin	Ref.		
Etoposide plus carboplatin	0.93	0.717–1.319	0.86

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; N, denominator.

Patients younger than 70 years (179 patients) had a mOS of 7.73 months (95% CI 6.77–8.69), whereas 165 patients older than 70 years had a mOS of 6.35 months (95% CI 5.23–7.47), which was statistically significant (*P*=0.004, log-Rank [Mantel-Cox]). We compared treatment separately for the over and under 70 years age groups. In the under 70 years group, 55 patients treated with cisplatin combination with an mOS of 7.73 months (95% CI 4.19–11.27) and 124 patients treated with carboplatin combination with the same mOS of 7.73 months (95% CI 6.98–8.48); the groups did not differ statistically in survival (*P*=0.283, log-rank [Mantel-Cox]).

In the group of patients aged 70 years and older, only 24 patients treated with the cisplatin combination had an mOS of 5.30 months (95% CI 2.89–7.71) and 141 patients treated with the carboplatin combination had mOS of 6.74 months (95% CI CI 5.42–8.06 months). This was not a statistically significant difference (*P*=0.224, log-rank [Mantel-Cox]).

A Cox regression model for OS was subsequently created for the observed parameters and the combination of chemotherapy used (Table 5). Taking into account the influence of the different distribution of selected parameter categories (PS, smoking, gender, age) between patient groups, no statistically significant difference in overall survival was observed between patients with the combination of etoposide + cisplatin and the combination of etoposide + carboplatin.

DISCUSSION

The analysis showed no statistically significant difference in mOS or mPFS depending on carboplatin or cisplatin in combination with etoposide. The difference in survival was also not statistically significant after stratifying patients by PS and age and according to the Cox regression model. We hope that analysing recent real world data can help clinicians with their choice of treatment for individual patients.

The effectiveness of cisplatin or carboplatin in combination with etoposide for patients with ES-SCLC was investigated by Rosi et al. in a 2012 meta-analysis. The authors of the meta-analysis concluded that these two platinum agents do not differ in mOS or mPFS in the ES-SCLC indication but differ in toxicity and spectrum of adverse events[17]. A retrospective analysis of patients with SCLC performed in 2022 from the US National Veterans Affairs Central Cancer Registry also showed no difference in overall survival of patients with ES-SCLC or LS-SCLC

depending on the use of cisplatin or carboplatin in chemotherapy combination, except for patients with ES-SCLC over 70 years of age who slightly benefited from the use of carboplatin[18]. Therefore, the same age limit of 70 years was used in our analysis when comparing treatment outcomes in different age groups.

Our analysis focused on previously unselected patients with ES-SCLC treated with chemotherapy in the Czech Republic and listed in the LUCAS project. Thus, we were able to include 348 patients in the analysis. Most patients in our cohort were treated with carboplatin, which seems to be related to its generally better tolerability and is in line with the current recommendations of the European Society for Medical Oncology and the National Comprehensive Cancer Network[19,20].

The overall survival of patients in our cohort is slightly lower than reported in the above mentioned studies investigating the treatment of patients with ES-SCLC, which may be due to the higher mean age and worse PS of patients in our cohort compared to most studies.

Carboplatin has significantly less frequent serious neurotoxic, ototoxic, nephrotoxic and gastrointestinal adverse effects but significantly more frequent haematotoxic effects[21-24]. Thus, the predicted toxicity and its effect on the patient is important for treatment selection.

Chemotherapy in ES-SCLC has a palliative purpose. It aims to prolong the life of patients, but mainly to alleviate the symptoms of the disease and thus improve the quality of life. There are few papers dealing with the quality of life of these patients, and the effect of the chosen treatment on symptoms and quality of life is thus assessed by each physician according to his/her own experience or based on the practices of a given institution. It would be interesting to focus further research on these aspects concerning the chosen treatment and thus support oncologists' decision-making in the choice of palliative treatment with additional data.

The limitations of this study are related to its retrospective nature with risk of bias. We are unaware of the criteria by which individual physicians choose a given chemotherapeutic combination. We did not analyse the number of cycles administred or possible delays between cycles of chemotherapy caused by adverse events. The cohort of patients was not very large and therefore maybe unable to find statistical difference in efficacy of treatment for subgroup of patients (i.e. only 24 patients over 70 years was treated with cisplatin).

CONCLUSION

Platinum-based chemotherapy has been used in treatment for four decades. Carboplatin and cisplatin are similar agents that share the same mechanism of anticancer action but differ in efficacy in different indications and the spectrum of adverse effects.

Our retrospective analysis of a cohort of 344 patients with ES-SCLC treated with chemotherapy showed no statistically significant difference in mOS or mPFS according to the use of carboplatin or cisplatin in combination with etoposide, and this result did not differ when patients were stratified by PS and age category. Moreover, no difference was observed using a Cox regression model including the effect of covariates.Since cisplatin and carboplatin differ mainly in their spectrum of adverse effects, the expected toxicity, the patient's performance status, age and comorbidities should play a role in drug selection.

ABBREVIATIONS

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ES-SCLC, extensive-stage small-cell lung cancer; HR, hazard ratio; IASLC, LS-SCLC, limited-stage small-cell lung cancer; mOS, median of overall survival; mPFS, median progression-free survival; ORR, overall response rate; OS, overall survival; PFS, progression free survival; PS, performance status; SCLC, small-cell lung cancer.

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Author contributions: AB: study design, literature search, manuscript preparation, patient selection MM: study design, manuscript revision and submission, patient selection ZC, LF, LFCM, OV, PJ, MC, MH, JK: patient selection, PD: statistical analysis, manuscript preparation and review MS: revision of the manuscript, final approval.

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