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Trends in response rate and survival in small-cell lung cancer patients between 1997 and 2017

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ABSTRACT

Introduction: Median survival of small-cell lung cancer (SCLC) patients is usually around 1 year. The advent of new drugs may have slightly improved their prognosis. We aimed to assess whether SCLC response to chemotherapy and survival had changed over time.

Methods: Consecutive SCLC patients were included at Grenoble University Hospital, France. We compared the patients' characteristics, response to chemotherapy and survival between 1997–2009 (period 1) and 2010–2017 (period 2).

Results: A total of 529 patients were identified, of whom 498 received a first line of chemotherapy and 279 a second line. The majority (n = 290, 58%) had extensive disease. The objective response rate (ORR) to first-line chemotherapy in metastatic patients was 63% in period 1 and 62% in period 2; the ORRs to second-line chemotherapy were 39% and 29%, respectively. Median overall survival from first-line chemotherapy was 13.2 months (interquartile range [IQR] 7.4–24.4) in period 1 and 11.2 months (IQR 7.1–21.2) in period 2. Mortality in these two periods did not differ significantly even after adjustment for prognostic factors (hazard ratio [HR] = 0.82, 95% confidence interval [CI] 0.66–1.00). The factors independently associated with death were cardiovascular comorbidities (HR = 1.28 [95%CI 1.05–1.55]), liver comorbidities (HR = 1.31 [95%CI 1.03–1.65]), poor ECOG performance status (3–4*vs.* 0–1, HR = 2.45 [95%CI 1.83–3.30]) and extensive disease (HR = 2.69 [95%CI 2.18–3.33]).

Conclusions: Since 1997, there has been no improvement in the survival or response rate to chemotherapy of SCLC patients. There is a desperate need for new approaches in this setting.

1. Introduction

Small-cell lung cancer (SCLC) represents 13 to 20% of lung cancer [1,3]. Tobacco consumption is the main risk factor for this disease. While the proportion diagnosed with SCLC has declined from approximately 20 to 13% in Europe [3], it has remained stable in the United States of America (USA) [2,3]. SCLC is often considered an incurable disease, with median survival being shorter than non-small cell lung cancer and less than 12 months at any stage [3]. In the last two decades, there has been no dramatic breakthrough in the clinical care of SCLC and survival has remained poor [3]. Schabath et al. [4] identified an increase in the median survival time of treated SCLC from 11.3 to 15.2 months. These two studies included patients up to 2010 and no data is available for subsequent patients with SCLC.

Two forms of the disease are distinguished in the TNM classification, namely extensive and limited SCLC [5]. The improvement of imaging, particularly with positron emission tomography (PET) [6], has made a better approach to the disease possible because all tumor sites

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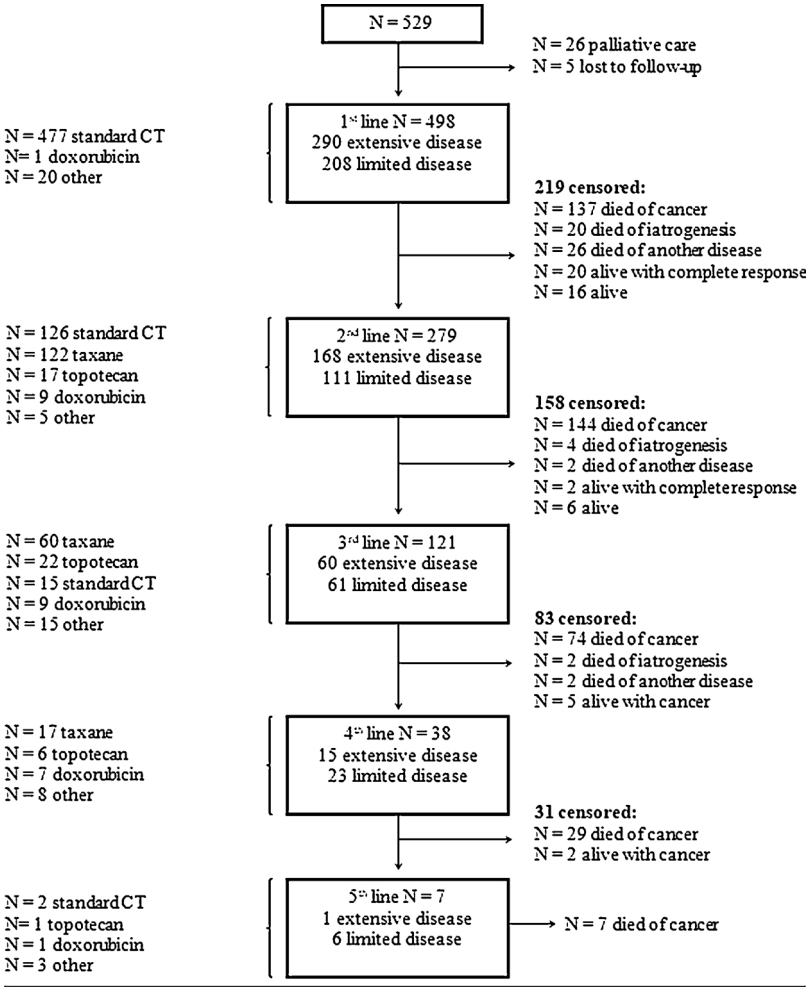

Fig. 1. Flow chart of study patients.

can be characterized. This has caused a decrease in the proportion of cases with limited SCLC [7]. Treatment is adapted to each patient depending on whether they have extensive or limited disease. Platinum-based chemotherapy (CT) remains the cornerstone of first-line treatment [8], and it is combined with thoracic radiotherapy in limited disease [9]. All limited cases should be considered for prophylactic cranial irradiation (PCI) [10] if they respond to initial treatment. For extensive cases, PCI should be discussed if there is disease stability or a disease response at the end of treatment, since it could prevent the development of brain metastases and improve patient survival [10].

Most patients relapse and second-line treatment depends on sensitivity to the first-line CT. Patients with sensitive relapse may derive benefit from a re-initiation of the first-line regimen [9]. Only topotecan is recommended in the second line [11]. Cyclophosphamide, doxorubicin and vincristine (CAV) is another option.

However, the advent of new regimens and the impact of supportive treatments may have slightly improved the prognosis of these patients. The aim of this study was to compare response to CT in two distinct periods between 1997 and 2017.

2. Material and methods

2.1. Study design and patients

All SCLC patients discussed during weekly thoracic oncology multidisciplinary team meetings at Grenoble Alpes university hospital, France, were selected. Any who required multidisciplinary expertise were presented. Metastatic cases have to be treated according to the guidelines only. This data has been entered into a database since 1980. This paper followed on from an initial analysis of 300 SCLC patients discussed between 1997 and 2009 [12]. We added patients discussed during our team meetings between 2010 and 2017. All patients who received at least one line of CT were included, those receiving supportive care only at diagnosis were excluded from the analysis.

The study obtained ethical approval on September 12, 2018 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891). An information letter was sent to each living patient, while we obtained an exemption from the obligation to inform deceased patients (from the CNIL, the French data protection agency).

Our primary objective was to identify the factors associated with a response to first- and second-line CT. The secondary objectives were to compare survival between period 1 (1997–2009) and period 2 (2010–2017) and to identify prognostic factors at the beginning of first- and second-line treatment.

2.2. Data collection

The following clinical data were collected at the time of diagnosis: sex, age, weight loss, Eastern Cooperative Oncology Group (ECOG) performance status (PS) [13], smoking history and cancer characteristics (histology, stage, and related paraneoplastic syndromes). Each antineoplastic treatment (CT, radiotherapy, and surgery) and the response to each treatment line were reported. Follow-up was completed for all patients in December 2017 using our hospital medical records or

a call to the place of birth.

Using the response to treatment (RECIST criteria [14]) at 3 months after the end of the first CT, we classified patients into three categories: "sensitive" if an objective response (a partial or complete response) was observed at 3 months, "resistant" if an initial objective response was observed but relapse occurred before 3 months, and "refractory" if no response was observed or progression occurred during treatment [15].

2.3. Statistical analysis

Data were expressed as number (and percentage) for qualitative variables and median (and interquartile range [IQR]) for quantitative variables and were compared between the two period groups using chi-squared or Mann-Whitney tests, as appropriate.

The potential risk factors associated with survival from the beginning of first- and second-line treatment were estimated using univariate Cox models. Multivariate Cox models adjusted for significant variables were computed with stepwise selection. We decided to stop the analyses after the second line because of limited patient numbers. For the multivariate models, missing data was imputed into the model.

All tests were two-sided, and P values < 0.05 were considered statistically significant. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient characteristics and anticancer treatment

A total number of 529 patients were identified (Fig. 1). Of these, 498 received a first line of treatment (477 [96%] with etoposide and platinum CT), 279 a second line (126 [45%] with etoposide and platinum CT and 122 [44%] with taxane-based CT), and 121 a third line.

The patients' characteristics are shown in Table 1. Median age was 64 years (IQR: 56–71), 116 (23%) were women, and 208 (42%) had limited-stage disease. The proportion of patients with weight loss of ≥ 10% at diagnosis was higher in period 2 (n = 50, 28%) compared to period 1 (n = 50, 18%) (p < 0.01). Concomitant or sequential mediastinal radiotherapy was performed in 96/148 (65%) limited SCLC patients in period 1 and in 41/60 (68%) in period 2. In period 1, 81 (26%) patients received PCI, as did 59 (33%) in period 2. Some 28 patients underwent surgery, in most cases (n = 16/18, 89%) before the diagnosis of SCLC. In the 10 remaining patients, the date of surgical resection was not available.

3.2. Objective response rates according to the line of chemotherapy

In metastatic patients, the objective response rates (ORRs) to first-line chemotherapy were 63% and 62% during periods 1 and 2, respectively (Table 1). Most patients (n = 226, 45%) were sensitive to first-line treatment, 121 (24%) were resistant, and 109 (22%) refractory. This response pattern was similar across the two periods. The ORRs to second-line treatment were 39% and 29% in periods 1 and 2, respectively, and those to third-line treatment were 19% and 20%.

Among those patients sensitive to first-line treatment, 144 (64%) were able to receive a second line with an ORR of 52% (n = 75), and 21 (9%) were still responding at the time of data analyses. Among resistant patients, 81 (67%) were able to receive a second line with an ORR of 20% (n = 16). Among refractory patients, 53 (49%) were able to receive a second line with an ORR of 13% (n = 37).

3.3. Factors Associated with survival

Median overall survival from the beginning of treatment was 12.2 months (IQR: 7.2–22.5), 13.2 months in period 1 (IQR: 7.4–24.4) and 11.2 months in period 2 (IQR: 7.1–21.2) (Supplemental Table 1).

Univariate and multivariate survival analyses from the beginning of

Table 1
Characteristics of Patients and Response to Chemotherapy according to Treatment Line.

	All patients N = 498	Diagnosis < 2010 N = 317	Diagnosis ≥ 2010 N = 181	*P* value
Patient characteristics				
Female	116 (23)	73 (23)	43 (24)	0.85
Age (years)	64 [56-71]	63 [55-71]	65 [58-72]	0.03
Smoking status (MD, n = 33)				
- Non-smoker	17 (4)	10 (4)	7 (4)	0.23
- Former smoker	158 (34)	89 (31)	69 (39)	
- Active smoker	290 (62)	187 (65)	103 (58)	
Comorbidities				
- Cardiovascular	245 (49)	151 (48)	94 (52)	0.36
- Respiratory	156 (31)	104 (33)	52 (29)	0.35
- Renal	62 (12)	45 (14)	17 (9)	0.12
- Hepatic	100 (20)	68 (22)	32 (18)	0.31
ECOG-PS (MD, n = 2)				0.15
- 0-1	278 (56)	181 (58)	97 (54)	
- 2	150 (30)	98 (31)	52 (29)	
- 3-4	68 (14)	36 (11)	32 (18)	
Weight loss ≥ 10% (MD, n = 35)	100 (22)	50 (18)	50 (28)	9.10^{-3}
Cancer characteristics				
Extensive disease	290 (58)	169 (53)	121 (67)	3.10^{-3}
Histology				
- Pure SCLC	453 (91)	289 (91)	164 (91)	0.83
- Combined SCLC	45 (9)	28 (9)	17 (9)	
Paraneoplastic syndrome				0.70
- None	424 (85)	270 (85)	154 (85)	
- Endocrinologic	8 (2)	4 (1)	4 (2)	
- Other	66 (13)	43 (14)	23 (13)	
1st line concurrent treatment				
Surgery	28 (6)	24 (8)	4 (2)	0.01
Radiotherapy				
- Mediastinal	141 (28)	99 (31)	42 (23)	0.06
ED/LD	4/137	3/96	1/41	
- Cranial prophylaxis	140 (28)	81 (26)	59 (33)	0.09
- Palliative	65 (13)	42 (13)	23 (13)	0.86
Response to 1st line CT				
ORR (MD, n = 13)	352 (73)	228 (74)	124 (71)	0.52
ORR in LD (MD, n = 4)	176/208 (86)	124/148 (86)	52/60 (88)	0.62
ORR in ED (MD, n = 9)	176/290 (63)	104/169 (63)	72/121 (62)	0.87
Sensitivity (MD, n = 42)				0.70
- Sensitive	226 (45)	150 (47)	76 (42)	
- Resistant	121 (24)	74 (24)	47 (26)	
- Refractory	109 (22)	68 (22)	41 (23)	
Response to 2nd line CT	**N = 279**	**N = 179**	**N = 100**	
ECOG-PS of 0-1 at the beginning of 2nd line (MD, n = 23)	136 (53)	88 (56)	48 (48)	0.19
Time between the beginning of 1st and 2nd lines (MD, n = 1)	9 [7–13]	10 [7–13]	9 [7–12]	0.18
ORR	99 (36)	70 (39)	29 (29)	0.09
DCR	154 (55)	99 (55)	55 (55)	0.96
Response to 3rd line CT	**N = 121**	**N = 81**	**N = 40**	
ECOG-PS of 0-1 at the beginning of 3rd line (MD, n = 11)	51 (46)	34 (49)	17 (43)	0.54
ORR	23 (19)	15 (19)	8 (20)	0.85
DCR	47 (39)	28 (35)	19 (48)	0.17

Data are expressed as median [IQR] for quantitative variables and as number (percentage) for qualitative variables.
DCR, disease control rate; ED, extensive disease; LD, limited disease; MD, missing data; ORR, objective response rate; PS, performance status; SCLC, small-cell lung cancer.

Table 2
Univariate and Multivariate Analyses of Factors Associated with Mortality from First-Line Chemotherapy.

	Univariate analysis	Multivariate analysis
Variable	**HR [95%CI]**	**HR [95%CI]**
2010-2017 *vs.* 1997-2009	1.03 [0.84-1.25]	0.82 [0.66-1.00]
Baseline patient characteristics		
Female *vs.* male	0.80 [0.64-1]	…
Age ≥ 60 years	1.21 [1-1.48]	…
Cardiovascular comorbidity	1.33 [1.1-1.6]	1.28 [1.05-1.55]
Respiratory comorbidity	1.19 [0.97-1.45]	…
Renal comorbidity	1.30 [0.98-1.72]	…
Hepatic comorbidity	1.66 [1.32-2.08]	1.31 [1.03-1.65]
ECOG-PS (MD, n = 2)		
- 0-1	1	1
- 2	1.81 [1.47-2.23]	1.35 [1.08-1.68]
- 3-4	3.40 [2.57-4.50]	2.45 [1.83-3.30]
Weight loss ≥ 10% (MD, n = 35)	1.70 [1.34-2.15]	…
Baseline cancer characteristics		
ED *vs.* LD	2.99 [2.44-3.67]	2.69 [2.18-3.33]
Paraneoplastic syndrome		
- None	1	…
- Endocrine	1.57 [1.20-2.06]	…
- Other	0.74 [0.33-1.65]	…
Etoposide-based CT *vs.* other CT	1.27 [0.68-2.39]	…

CT, chemotherapy; ED, extensive disease; LD, limited disease; MD, missing data.

Table 3
Univariate and Multivariate Analyses of Factors Associated with Mortality from Second-Line Chemotherapy (n = 278)*.

	Univariate analysis	Multivariate analysis
Variable	**HR [95%CI]**	**HR [95%CI]**
2010-2017 *vs.* 1997-2009	0.82 [0.64-1.07]	0.97 [0.73-1.27]
Baseline patient characteristics		
Female *vs.* male	0.80 [0.60-1.05]	…
Age > 60 years	1.01 [0.79-1.29]	…
Cardiovascular comorbidity	1.08 [0.84-1.38]	…
Respiratory comorbidity	1.30 [0.99-1.71]	…
Renal comorbidity	1.12 [0.74-1.70]	…
Hepatic comorbidity	1.23 [0.89-1.69]	…
Baseline cancer characteristics		
ED *vs.* LD	1.81 [1.4-2.33]	1.53 [1.17-2.01]
Paraneoplastic syndrome		
- None	1	…
- Endocrine	1.54 [1.08-2.2]	…
- Other	2.74 [0.87-8.62]	…
1st line characteristics		
Mediastinal radiotherapy	0.53 [0.4-0.71]	
Prophylactic cranial irradiation	0.59 [0.45-0.77]	
Palliative irradiation	1.67 [1.16-2.41]	
Sensitivity (MD, n = 2)		
- Sensitive	1	1
- Resistant	2.14 [1.6-2.86]	1.67 [1.19-2.35]
- Refractory	2.77 [1.99-3.85]	1.74 [1.17-2.61]
2nd line characteristics		
ECOG-PS ≥ 2 (MD, n = 22)	3.06 [2.33-4.01]	2.61 [2.00-3.41]
2nd line CT		
- Etoposide	1	1
- Taxane	2.61 [2.00-3.41]	1.54 [1.10-2.16]
- Other	1.69 [1.20-2.56]	1.09 [0.67-1.76]

CT, chemotherapy; ED, extensive disease; LD, limited disease; MD, missing data.

* One patient with unknown date of second line start was excluded.

first-line CT are reported in Table 2. Mortality did not differ significantly across the two periods, even after adjustment for prognostic factors (hazard ratio (HR) = 0.82; 95% confidence interval [CI] 0.66–1.00). Factors independently associated with mortality were cardiovascular comorbidity (HR = 1.28 [95%CI 1.06–1.55]), liver comorbidity (HR = 1.29 [95%CI 1.02–1.63]), ECOG PS (2 *vs.* 0–1, HR = 1.35 [95%CI 1.08–1.68]; 3–4 *vs.* 0–1, HR = 2.45 [95%CI 1.83–3.30]), and extensive disease (HR = 2.67 [95%CI 2.17–3.29]). Fig. 2 represents this Cox adjusted survival curve.

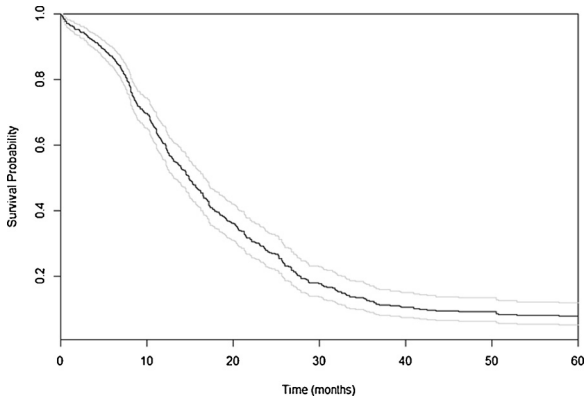

Fig. 2. Cox adjusted survival curve from the beginning of first-line chemotherapy. Adjustment was performed with variables associated with survival (Table 3): ECOG performance status, extensive *versus* limited disease, cardiovascular comorbidities, and liver comorbidities.

From the beginning of second-line CT (Supplemental Table 1), the factors independently associated with mortality were extensive disease at diagnosis (HR = 1.52 [95%CI 1.17–1.99]), sensitivity to first-line CT (HR = 1.74 [95%CI 1.17–2.61] and HR = 1.67 [95%CI 1.19–2.35] for refractory *vs.* sensitive and resistant *vs.* sensitive, respectively), ECOG PS ≥ 2 at the beginning of second-line treatment (HR = 2.6 [95%CI 2–3.4]), and the CT agents used in the second line (HR = 1.55 [95%CI 1.11–2.17] and HR = 1.1 [95%CI 0.68–1.77] for taxane *vs.* etoposide CT and other *vs.* etoposide CT, respectively). Fig. 3 represents this Cox adjusted survival curve according to sensitivity to first-line CT.

3.4. Impact of tobacco use

In this study, 448 patients were smokers, of whom 158 (34%) were former smokers and 290 (62%) were active smokers. Never-smokers had poorer survival (Supplemental Table 1) with their median survival being 8.3 months (IQR: 3.0–12.2], as against 12.3 months (6.5–24) for former smokers and 12.2 months (7.4–22.4) for active smokers.

4. Discussion

This study highlights the lack of improvement in response to CT and survival over the last two decades. No change in the CT agents used was observed. Etoposide and platinum remain the standard CT. In our

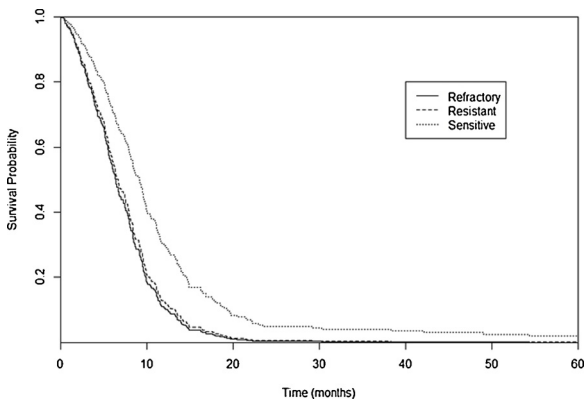

Fig. 3. Cox adjusted survival curve from the beginning of second-line chemotherapy. Adjustment was performed with variables associated with survival (Table 3).

center, we often used taxane CT in the second line even though this drug has never been registered for this setting.

The strength of this study was the variety of data recorded in a large number of patients, such as the ECOG PS at the beginning of each line of CT as well as the response thereto. But only the data of patients discussed at our weekly thoracic oncology multidisciplinary team meetings were reported. That explains why a large majority of patients received CT. Furthermore, this study was conducted in real life conditions, and so disease response was evaluated by the physicians in charge of the patients without external control. We were not able to specify which patients were staged by 18-fluoro-deoxyglucose (FDG)-PET, nor were we able to provide progression-free survival data for each line of CT.

Our patients had similar characteristics to those reported in the study by the French College of General Hospital Respiratory Physicians (KBP-2010-CPHG [16]). Namely, 23% were women, median age was 65 years, the proportions of never, former, and active smokers were the same, 55–60% had an ECOG PS of 0–1, and 70% had extensive disease. In other countries, some of these characteristics differ. In the United Kingdom [17] and the USA [4], women made up half of SCLC patients, and age at diagnosis was older (68 years). Interestingly, in the study by Schabath et al., half of patients had limited-stage disease in the 2000–8 period. Two patients' characteristics significantly differed between the 2 studied periods. We observed more patients with weight loss of $\geq$ 10% at diagnosis in the period 2, it could be due to a better nutritional evaluation over the last decade. Advances in imaging, as the systematic use of the 18-FDG-PET to confirm the absence of metastasis could explain that fewer patients had a localized disease in period 2.

Comorbidity among patients with SCLC is very common and has been increasing [18]. As in our study, Aarts et al. identified heart disease as having a negative prognostic effect on SCLC patients [18]. We also identify liver comorbidity as prognostic factor, but, to our knowledge, it is not describe in the literature. These results encourage identifying and stabilizing cardiac and liver comorbidities when starting chemotherapy in order to avoid more toxicity during the treatment. SCLC in never-smokers is an uncommon but highly aggressive disease. Never-smokers had clearly shorter survival (8.3 months *vs.* 12.3 months in former smokers and 12.2 months in active smokers). This survival data were similar to other studies, even in limited-stage disease [19].

In the SEER database, nearly half of SCLC patients were treated. Additional therapy beyond platinum CT was associated with survival benefit [20]. These results are consistent with ours. Khakwani et al. [17] observed an increase in the proportion of patients receiving both CT and radiotherapy each year (from 19 to 40% in limited disease and 9–21% in extensive disease between 2004 and 2011). As explained above, we are not able to provide this information.

In our study, the ORR to first-line CT (mostly etoposide and platinum) was 73%. It was 67% in patients treated with cisplatin and 66% in those treated with carboplatin in the Rossi study [8]. Regarding sensitivity, 45% of our patients were platinum-sensitive, as in a previous study [21], and the ORRs to second- and third-line treatment were 36 and 19%, respectively, without significant changes over time, while the disease control rates (DCRs) with second- and third-line treatment were 55 and 39%, respectively. In a retrospective study [22] reporting disease response among 193 patients treated in the second line with platinum-based CT (mainly irinotecan or topotecan) or a single-agent therapy, the ORR was 25% in the combination group and 9% in the single-agent group, while in that study the DCRs were 65 and 35%, respectively. In the second-line setting, the ORR to topotecan has been 24%, and that to CAV 18% [11]. In the study by Aktas et al. [21], the DCRs at first, second, and third-line CT were 92, 68, and 44%, respectively. In contrast to our study, only 14% of primary-resistant patients were able to receive second-line CT.

From the beginning of second-line CT, we identified extensive disease at diagnosis, first-line sensitivity, a poor ECOG PS, and the second-line drugs used as being associated with mortality. These results are consistent with the study published by Song et al. [22] in which PS, recurrence type and further treatment were independently associated with survival on second-line treatment. An anti-PD1 (Nivolumab) was granted FDA approval in 2018 for the treatment of patients with SCLC with disease progression following platinum-based CT and one other line of therapy. Rovalpituzumab (in the first, second and third lines) [23] and Alisertib in combination with Nab-paclitaxel (in the second line) are new drugs being developed in SCLC.

5. Conclusions

Since 1997, there has not been any improvement in response rates to CT or survival in SCLC patients. There is a desperate need for new approaches in this setting. Various ongoing clinical trials and the recent FDA approval of Nivolumab in SCLC are encouraging signs.

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Appendix A. Supplementary data

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