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Phase III study of cyclophosphamide, doxorubicin, and etoposide compared with carboplatin and paclitaxel in patients with extensive disease small-cell lung cancer ☆,☆☆

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ABSTRACT

The progression-free survival (PFS) of cyclophosphamide/doxorubicin/etoposide (CDE) and carboplatin/paclitaxel (CP) was compared in chemonaive patients with extensive disease small-cell lung cancer (ED-SCLC). A total of 203 patients were randomised to three-weekly CDE ($n = 102$) or CP ($n = 101$) for five cycles. Tumour response rates in CDE and CP were 60% and 61%. PFS of CP was 5.2 months, PFS of CDE 4.9 months ($p = 0.60$). The major difference in toxicity between CDE and CP was grade 4 leukocytopaenia in 64% and 9% of the patients ($p < 0.0001$), leading to febrile neutropaenia in 30% and 4% of the patients ($p < 0.0001$), respectively. This was the reason for differences in the total number of hospital admissions (63 for CDE and 40 for CP, $p = 0.0025$).

This study failed to demonstrate any benefit in PFS with CP compared with CDE. CP was associated with significantly less haematological toxicity, leading to 37% less hospital admissions for febrile neutropaenia.

1. Introduction

Until recently, cyclophosphamide, doxorubicin, and etoposide (CDE) was commonly used for patients with extensive disease small-cell lung cancer (ED-SCLC) in the European Union. This schedule was based on large studies conducted by the European Organization for Research and Treatment of Cancer (EORTC)-Lung Cancer group.[1–3] In these studies, a tumour

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response rate of 79%, a median time to progression of 5.8 months, and a median survival time of approximately 8 months were observed. The major toxicity of CDE is myelosuppression, which is associated with febrile leukopaenia in about 30% of the patients.[4]

In North America, the preferred treatment for SCLC is a platinum-containing combination.[5] Multiple agents have been combined with either cisplatin or carboplatin, such as etoposide,[6] irinotecan or topotecan,[7–9] or pemetrexed.[10] In phase II studies, carboplatin with paclitaxel (CP) was effective as first- and second-line treatment in ED-SCLC,[11–13] but this doublet has never been compared to other regimens. Based on previously observed high response rates and mild toxicity for carboplatin (area under the curve (AUC) of 7) and paclitaxel (175 mg/m^2) as second-line treatment,[11] a similar regimen was chosen as first-line treatment.

In the present phase III study, the efficacy of CP and CDE as first-line treatment for ED-SCLC was compared.

2. Patients and methods

2.1. Patients

Patients were included if they met all the following criteria: age over 18 years, histologically or cytologically proven ED-SCLC with measurable or evaluable lesions, no prior chemotherapy or radiotherapy except for symptomatic brain metastases, Eastern Cooperative Oncology Group (ECOG) performance score 0–2, adequate haematological, renal and hepatic functions (absolute neutrophil count (ANC) $\geqslant 2.0 \times 10^9$/L, platelet count $\geqslant 100 \times 10^9$/L, bilirubin $\leqslant 1.25 \times$ upper normal limit, creatinine clearance according to Cockroft formula $\geqslant 60$ ml/min). Patients were excluded if they had cardiac failure, pre-existent peripheral neuropathy, hypersensitivity to castor oil, uncontrolled infection, other malignant disease, or if they were pregnant or breast-feeding. Radiotherapy was allowed as long as at least one measurable lesion was outside the irradiated field. No other anticancer drugs were allowed. The protocol was approved by all local medical ethics committees, and all patients gave written informed consent.

2.2. Treatment and dose modifications

Cyclophosphamide (1000 mg/m^2) was administered intravenously on day 1, doxorubicin (45 mg/m^2) on day 1, and etoposide (100 mg/m^2) on days 1, 2, and 3. Carboplatin (AUC 7 using the Calvert formula[14]) was administered intravenously on day 1 followed by paclitaxel (175 mg/m^2) as a 3-h infusion.

Cycles were repeated every 3 weeks, with a maximum of 5 cycles. Patients were retreated if leucocytes $\geqslant 3 \times 10^9$/L and platelets $\geqslant 100 \times 10^9$/L. Otherwise, treatment was delayed for one week. If the delay was more than two weeks, patients went off-study.

All drugs in both regimens were 25% reduced if ANC $<0.5 \times 10^9$/L and/or platelets $<50 \times 10^9$/L for two consecutive counts one week apart, and in case of febrile neutropaenia or severe bleeding. If despite this dose reduction grade III or IV toxicity occurred, patients went off-treatment. In the event of grade III or IV non-haematological toxicity (excluding alopecia, nausea, and vomiting), both regimens were reduced by 25%. In case of grade III or IV neurological toxicity or a severe hypersensitivity reaction, patients went off-treatment.

Treatment was stopped for intolerable toxicity, treatment delay of more than two weeks, progressive disease, or on patient's request. The mean relative dose intensity was calculated by dividing the actual delivered dose (mg/m^2/week) by the planned dose (mg/m^2/week) for the number of cycles each patient received.

2.3. Evaluations

Before chemotherapy, patients were evaluated with a history, physical examination, ECOG performance status, complete blood cell count (CBC), electrolytes, liver enzymes, serum creatinine and electrocardiography (ECG), which were all repeated before every next cycle, except for the ECG. On day 14 of each cycle and on clinical indications, a CBC was performed in a similar way in both arms. Tumour evaluations were performed with a computed tomography (CT)-scan of the chest and repeated after two cycles and at the end of treatment. Tumour response was defined according to the WHO criteria.

Follow-up after treatment was every 4–6 weeks with a CBC, liver enzymes, chest X-ray, or additional tests if clinically indicated. Toxicity was scored before each cycle according to the National Cancer Institute Common Toxicity Criteria (CTC), version 2.0.

2.4. Statistics

All patients were randomised by telephone at the Trial Office and checked for their eligibility. Stratification was performed according to institute and performance status (0–1 versus 2) using the minimisation technique.[15]

This study was powered to detect a 50% increase in median time to progression (i.e. from 5.8 to 8.7 months), using a two-sided 0.05 α-level test with 80% power. The primary objective was progression-free survival (PFS). Efficacy of chemotherapy is better evaluated by PFS than by overall survival, because subsequent second-line chemotherapy can subsequently prolong survival.[16] Secondary objectives were overall survival, tumour response rates, duration of response and safety.

All analyses were performed on the intention-to-treat principle. Patients remained on study till death or loss of follow-up. The database was closed on July 1, 2006.

Progression-free survival was defined as the interval from the date of start of treatment to the date of progression or death from any cause. Overall survival was calculated from the date of randomisation till the date of death or censored at the end of study. Duration of response was defined as time from documentation of tumour response until progression.

Patient characteristics and toxicity scores were compared using Mann–Whitney U or χ^2 tests, as appropriate. Differences in severity of haematological toxicity between the two arms were tested with the Cochran–Armitage trend test. Differences between Kaplan–Meier survival curves were tested with log-rank test.

3. Results

3.1. Patient characteristics

From February 1999 to February 2005, 203 patients were randomised to either CDE ($n = 102$) or CP ($n = 101$). Two patients could not be evaluated for dose intensity and toxicity (one patient received one cycle of CDE, but data are missing and one patient randomised to CP never started therapy). One patient randomised to CDE received five cycles of CP. Patient characteristics were well balanced in the two arms (Table 1).

3.2. Delivery of treatment

A total of 374 cycles were administered to patients randomised to treatment with CDE and 384 cycles to patients randomised to treatment with CP. Median number of cycles was 5 for both groups. This maximum number of cycles was achieved in 56% of patients treated with CDE and in 51% of patients treated with CP. At least 3 cycles of chemotherapy were administered to 72% of patients in the CDE group and 74% in the CP group. Reasons for treatment discontinuation were similar in both groups, with unacceptable toxicity, progressive disease and non-treatment related death as most common reasons.

In the CDE group, 39 of 374 cycles (10%) were delayed, in the CP group 62 of 384 cycles (16%) were delayed ($p = 0.027$). In both treatment arms, 20% of patients had a dose reduction of one or more drugs. The mean relative dose intensities for CDE were 93.9% for C, 91.7% for D and 94.2% for E, and for the CP schedule 93.1% for C and 93.3% for P. The average mean dose intensity was not different between CDE and CP (both 93%).

3.3. Tumour response and survival

Forty-four patients (22%) could not be evaluated for tumour response (23 in CDE group, 21 in CP group), because of early end of treatment due to toxicity ($n = 31$), non-treatment related death ($n = 5$) or other reasons ($n = 8$). Overall tumour response rate was similar for the CDE group (60%, 95% CI, 50–69) and the CP group (61%, 95% CI, 51–71) (Table 2).

No difference in efficacy between CDE and CP schedules was observed in patients with age over 65 versus younger patients, patients with performance score $\geqslant 2$ versus patients with performance score $\leqslant 1$, or between males and females.

Median PFS for patients treated with CDE was 4.9 months (95% CI, 3.5–5.7), that is not different from those treated with CP (5.2 months, 95% CI, 4.8–5.7) (Fig. 1). Median duration of tumour response for complete or partial responders was not different between both treatment groups (6.5 months for CDE ($n = 61$) and 5.6 months for CP ($n = 62$), $p = 0.425$). Overall survival for patients with CDE was 6.8 months (95% CI, 5.3–8.9, 1-year survival 24%) and for CP 6.7 months (95% CI, 5.9–8.7, 1-year survival 26%) (Fig. 2).

Table 1 – Patient characteristics

Characteristic	CDE ($n = 102$)	CP ($n = 101$)
Age (year)		
Median	61.7	62.7
Range	37–77	42–84
Sex		
Male	55 (54%)	63 (62%)
Female	47 (46%)	38 (38%)
ECOG performance score		
0	17 (17%)	21 (21%)
1	66 (65%)	57 (56%)
2	19 (19%)	22 (22%)
Missing	0	1 (1%)
Prior radiotherapy	6 (6%)	1 (1%)
Any comorbidity	50 (49%)	48 (48%)
Pulmonary	9 (9%)	16 (16%)
Cardiac	21 (21%)	24 (24%)
Diabetes mellitus	14 (14%)	6 (6%)

ECOG, Eastern Cooperative Oncology Group; CDE, cyclophosphamide, doxorubicin, etoposide; CP, carboplatin and paclitaxel.

Table 2 – Tumour response rate evaluated with CT-scans in ED-SCLC patients

Response	CDE ($n = 102$)		CP ($n = 101$)	
	Number of patients	%	Number of patients	%
Complete response	13	13	14	14
Partial response	48	47	48	48
Overall response (CR + PR)	61	60	62	61
Stable disease	6	6	8	8
Progressive disease	12	12	10	10
No evaluation*	23	22	21	21

CDE, cyclophosphamide, doxorubicin, etoposide; CP, carboplatin and paclitaxel; CR, complete response; PR, partial response.
* Reasons for no evaluation were early end of treatment due to toxicity ($n = 31$), non-treatment related death ($n = 5$) or other ($n = 8$).

3.4. Toxicity

Overall, 201 patients were assessable for toxicity. Patients receiving CDE had significantly more episodes of grade IV leukocytopaenia (65 versus 9 patients, $p < 0.0001$), leading to febrile neutropaenia in 31 versus 4 patients ($p < 0.0001$). Patients treated with CDE were more often hospitalised (63 versus 40 patients, $p = 0.0025$). Infections, dyspnoea and pain were the most common reasons for hospitalisation. Seven patients in CP group had very mild hypersensitivity reactions which were easily managed during infusion. Most other toxicities (haematological and non-haematological) were equally distributed between the two groups (Table 3).

Treatment-related death occurred in eight patients treated with CDE and in one patient treated with CP ($p = 0.035$), in all but two patients occurring during the first cycle of chemotherapy. Neutropaenic sepsis was the cause of death in all patients.

4. Discussion

In the present phase III study, comparing CP versus CDE as first-line treatment for ED-SCLC, CP did not result in a longer PFS and overall survival compared to CDE. In both groups

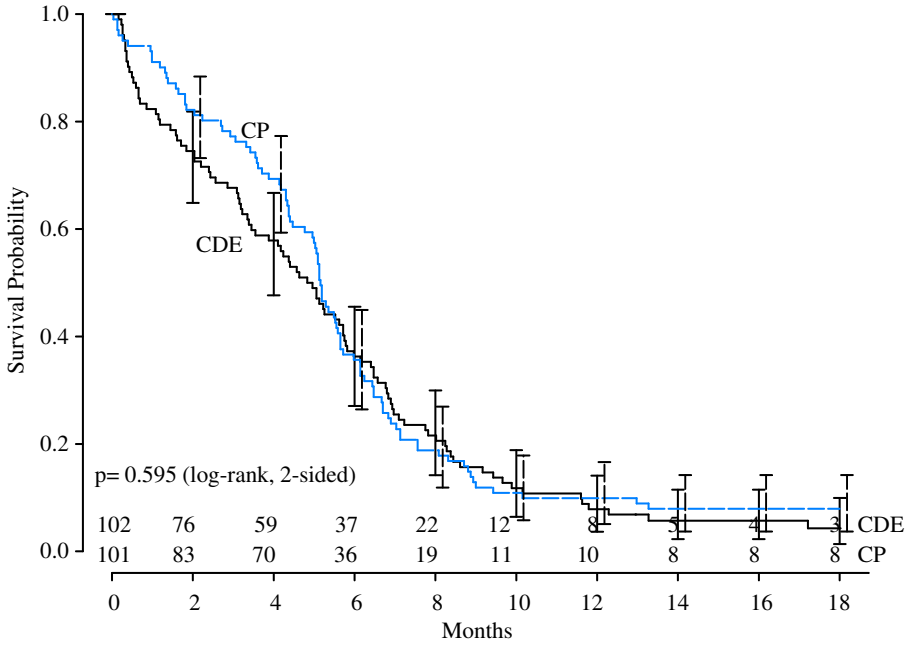

Fig. 1 – Progression-free survival in 203 patients with ED-SCLC treated with CDE or CP. CDE, cyclophosphamide, doxorubicin, etoposide; CP, carboplatin and paclitaxel.

about half of the patients completed the five planned cycles of treatment, but the toxicity profile of CDE was worse, reflected by a higher number of neutropaenic fever episodes and hospitalisations.

CP has never been directly compared with the CDE regimen in ED-SCLC. Our results in patients treated with CDE were consistent with results observed in previously reported studies (tumour response rates 52–73%, progression-free survival 5.8 months and overall survival 7.6–8.7 months).[1–3,17] CP as doublet regimen has been studied in several phase II studies, with slightly different treatment regimens as compared to our regimen. Thomas and colleagues treated patients with carboplatin AUC 6 and paclitaxel 200 mg/m^2 every three weeks,[12] with a response rate of 65%, and a median overall survival of 8.7 months. With carboplatin AUC 6 and paclitaxel 175 mg/m^2 every 4 weeks, a response rate of 54%, a median time to progression of 5.7 months and a median overall survival of 9.7 months were observed.[13] Both regimens had a tol-

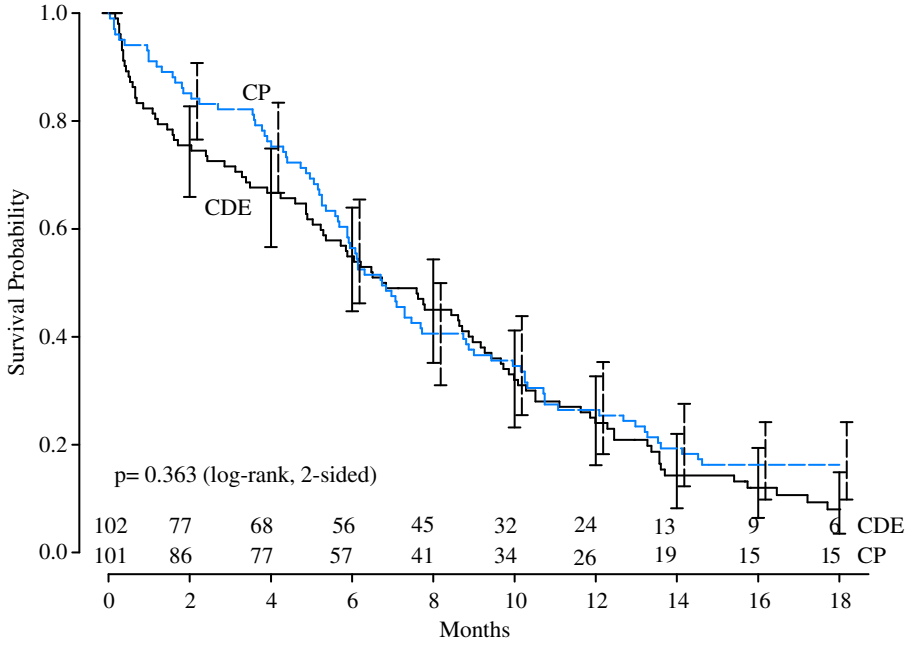

Fig. 2 – Overall survival in 203 patients with ED-SCLC treated with CDE or CP. CDE, cyclophosphamide, doxorubicin, etoposide; CP, carboplatin and paclitaxel.

Table 3 – Grades III and IV haematological and non-haematological toxicity in ED-SCLC patients

Toxicity	CDE (n = 101)	CP (n = 100)
Haematological		
Anaemia		
Grade III	20	9
Grade IV	3	3
Thrombocytopaenia		
Grade III	27	20
Grade IV	2	2
Leukopaenia*		
Grade III	26	24
Grade IV†	65	9
Neutropaenia*		
Grade III	12	23
Grade IV†	37	16
Non-haematological		
Haemorrhage	5	1
Cardiac toxicity	3	5
Fatigue	13	9
Myalgia	0	5
Anorexia	6	3
Diarrhoea	4	3
Nausea	6	4
Vomiting	3	5
Infection†	28	3
Neurotoxicity	9	6
Pulmonary toxicity	14	18
Alopecia (grade II)	50	47
Other toxicity	19	15
Hypersensitivity reactions (any grade)†	0	7
Febrile neutropaenia†	31	4

CDE, cyclophosphamide, doxorubicin, etoposide; CP, carboplatin and paclitaxel.
* Leukopaenia and neutropaenia were more common and more severe in CDE group ($p < 0.0001$ and $p = 0.016$, respectively, Cochran–Armitage trend test).
† $p < 0.01$ (χ^2 test).

erable toxicity profile. Using paclitaxel 200 mg/m^2 and carboplatin AUC 6 every three weeks, an overall response rate of 61% and a median survival of 11.8 months in patients with ED-SCLC were reported.[18] CP as a second-line treatment yielded a response rate of 74% and a median time to progression of 4.8 months.[11] In summary, the results of the first comparative study further define the therapeutic performances of CDE and CP regimens, both resulting in a median progression-free survival of approximately 5 months and a response rate around 60% for ED-SCLC.

With CP and CDE showing an equal efficacy in ED-SCLC, toxicity and safety are major issues in treatment decisions. The toxicity profile of CP was significantly better than that of CDE. More treatment-related deaths were observed in the CDE group compared to the CP group. This was mainly caused by the higher number of grade IV leukocytopaenia in CDE, resulting in more hospitalisations for treatment complications. The CP regimen did not result in more grades III and IV neurotoxicity than the CDE regimen. The 8% treatment-related deaths for CDE treatment is not significantly different from previously reported studies (2–7%),[1–4,17,19] and one should realise that all patients had ED, which is regarded as a risk factor for treatment-related death.[4,17] Treatment-related death was most common during the first cycle of chemotherapy, as was previously described.[4,19] Standardised use of prophylactic antibiotics and/or granulocyte colony-stimulating factors might decrease this toxic death rate,[19] as recommended by the 2006 American Society of Clinical Oncology (ASCO) and EORTC guidelines.[20,21] Despite a higher toxicity observed in the CDE treatment arm, the percentage of patients that completed the planned five cycles of chemotherapy was equal in both groups.

In conclusion, the present study failed to demonstrate any benefit in terms of PFS with CP compared to CDE. CP has a more favourable toxicity profile than CDE. Given the results of the present study, CDE should no longer be used as first-line treatment for ED-SCLC, with CP being a good alternative treatment combination.

Conflict of interest statement

We declare that no conflict of interest exists for any of the authors.

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