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Original Paper

Standard Versus Alternating Non-cross-resistant Chemotherapy in Extensive Small Cell Lung Cancer: An EORTC Phase III Trial

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Alternating chemotherapy for small cell lung cancer has been tested in several studies. Some have shown positive results that have not been confirmed in other studies. In all of the studies, however, the degree of non-cross-resistance in the regimens was questionable. The EORTC Lung Cancer Study Group developed two equipotent regimens: (i) standard (CDE)—cyclophosphamide, doxorubicin, etoposide; (ii) (VIMP)—vincristine, carboplatin, ifosfamide, mesna, both non-cross-resistance. These two combinations were alternated and compared with the standard chemotherapy regimen in a group of 143 patients with extensive small cell lung cancer. Median survival was 7.6 months in the standard arm and 8.7 in the alternating arm ($P = 0.243$). Median time to progression was 5.8 and 6.4 months, respectively ($P = 0.166$). Median response duration was 7.0 and 6.8 months ($P = 0.221$). The use of two alternating regimens with a proven degree of non-cross-resistance did not result in any improvement in survival in patients with extensive small cell lung cancer.

Key words: SCLC, alternating chemotherapy, non-cross-resistance
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INTRODUCTION

DURING THE last two decades, chemotherapy has become the cornerstone of treatment of small cell lung cancer (SCLC). This has resulted in improvement from the very short median survival in patients with untreated extensive SCLC [1] to median survival periods of approximately 9 months. For limited cases of the disease even cure is possible in 10–15% of patients. Several attempts to improve this result have been undertaken. One approach that is frequently tested is the use of two so-called non-cross-resistant chemotherapy regimens. This approach is based on the simple mathematical model of probability for the development of resistant cell clones within a tumour, proposed by Goldie and Coldman [2]. The model assumes that tumours grow exponentially and each course of chemotherapy results in log cell kill. The outcome in two treatment strategies, alternation of two non-cross-resistant drugs and sequential administration of therapy, was compared by computer simulation. Assuming that there was symmetry between the regimens, i.e. the same log cell kill and the same rate of mutation into cells resistant to the drugs used, alternating chemotherapy resulted in a greater cure rate compared with that of sequential therapy. The clinical experience with Hodgkin's disease makes it worth testing this Goldie–Coldman hypothesis [3] in SCLC.

In a previous study by the EORTC Lung Cancer Cooperative Group (LCCG) the standard chemotherapy regimen (cyclophosphamide, doxorubicin, etoposide) was compared with a regimen containing carboplatin [4]. Both regimens were found to be equipotent with regard to response rate, response duration and survival. In a later study, the degree of non-cross-resistance in both regimens was tested. Patients

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that were progressing, or within 3 months of stopping, the first line regimen, were treated with the other regimen. This resulted in 60% responses in those progressing during or shortly after cyclophosphamide, doxorubicin, etoposide and then treated with vincristine, ifosfamide and carboplatin. Patients initially treated with either carboplatin–vincristine or carboplatin–ifosfamide were treated at progression, during or after chemotherapy, with cyclophosphamide, doxorubicin and etoposide. This resulted in a response rate of 51% [5]. With these two equipotent regimens, both with a certain degree of non-crossresistance, the Goldie–Coldman hypothesis was tested in a randomised phase III study. The alternating regimen was compared with the standard chemotherapy regimen.

PATIENTS AND METHODS

Patients

From September 1988 until February 1992, 148 patients were entered into the EORTC trial 08882. All patients had histologically or cytologically proven SCLC. Eligibility criteria were: no previous chemotherapy, normal renal function (creatinine clearance > 60 ml/min), normal bilirubin levels (< 25 μmol/l), an ECOG (Eastern Cooperative Oncology Group) performance score ≤ 3, age < 75 years, normal numbers of leucocytes ($> 3 \times 10^9$/l) and platelets ($> 100 \times 10^9$/l), extensive disease. Informed consent was obtained from all patients.

Staging

All patients underwent routine staging procedures, including physical examination, a chest X-ray, standard or computer tomography (CT) of the chest, bronchoscopy, ultrasound, CT of the abdomen, an isotope bone scan, neurological examination, bone marrow biopsy, routine full blood cell counts, and tests on serum electrolytes and liver and renal function. Patients with disease outside one hemithorax, and mediastinal or supraclavicular nodes were considered to have extensive disease (ED). Further staging procedures were considered optional if one of the procedures revealed ED. Therefore, not all patients underwent all investigations. Restaging included all investigations that were initially abnormal.

Therapy

Patients were stratified according to the institution and performance status (0 versus 1 versus 2 versus 3). Standard therapy (CDE) was 1 g/m^2 cyclophosphamide given intravenously on day 1, 45 mg/m^2 doxorubicin given intravenously on day 1, and 100 mg/m^2 etoposide given intravenously on days 1, 3 and 5. A maximum of five courses were given, at 3

Table 1. Patient characteristics at entry by treatment arm

	Standard treatment with CDE	Alternating treatment with CDE+VIMP
Number	73	70
Median age in years (range)	61 (41–73)	61 (29–74)
Male/female	62/11	55/15
Performance status		
0	18	20
1	30	29
2	20	19
3	5	2
Bone marrow involvement		
No	38	36
Yes	10	18
Unknown	25	16
Brain metastases		
No	41	42
Yes	4	2
Unknown	28	26
Liver metastases		
No	36	23
Yes	35	31
Unknown	2	16
Bone metastases		
No	55	44
Yes	10	18
Unknown	8	8
Number of documented sites (liver, bone, bone marrow, brain)		
0	14	16
1	46	34
2	9	14
3	4	6

CDE, cyclophosphamide, doxorubicin, etoposide; VIMP, vincristine, carboplatin, ifosfamide, mesna.

week intervals between courses. Alternating therapy (VIMP) was 2 mg vincristine given intravenously as a bolus dose on days 1 and 8, 400 mg/m^2 carboplatin dissolved in 250 ml 5% dextrose and given as a 30 min intravenous infusion, 5 g/m^2 ifosfamide given as a 24 h infusion, and 0.6 g/m^2 mesna given as an intravenous bolus with 200 ml mannitol (20%) before the infusion with ifosfamide. During the ifosfamide infusion and over the following 12 h, 3.75 g/m^2 of mesna was given as a continuous infusion. Forced diuresis was established by giving 6 l of dextrose/saline in 38 h. In the alternating chemotherapy arm, CDE was given during courses 1, 3 and 5 and VIMP during courses 2 and 4. The interval between CDE and VIMP was 3 weeks and between VIMP and CDE 4 weeks.

Response and toxicity

Response was evaluated after each course of treatment by measuring the target lesion defined before the start of chemotherapy. At the end of the planned five cycles of chemotherapy, more extensive evaluations were carried out. Tumour response was defined according to standard criteria of the World Health Organisation (WHO). Response duration was measured from randomisation until progression and survival from randomisation until death. Toxicity was graded according to standard WHO criteria and scored after each course.

Statistical consideration

The main endpoint of the study was survival. The expected median survival in the standard arm was 9.2 months (based on the results of EORTC trial 08825 [6]). An increase to 1 year in median survival in the alternating chemotherapy arm would be considered clinically worthwhile. In order to detect such a benefit (with a power of 80% using a one-sided significance level of 5%), 180 patients were needed in each arm or follow-up until death.

Randomisation was carried out using the minimisation technique [7], stratifying patients according to their institution and performance status (0 versus 1 versus 2 versus 3). Duration of survival, time to progression and duration of response (complete and partial responders taken together for the time interval between the date of randomisation and the date of disease progression) curves were estimated using the Kaplan–Meier technique [8].

Although the sample size calculation was based on a one-sided type I error, all comparisons were performed using a two-sided logrank test. The Cox proportional hazards regression model [9] for survival was used to test for the treatment after adjustment for possible prognostic factors (age, albumin level, sex, performance status, levels of SGOT serum glutamic oxaloacetic transaminase, SGPT serum glutamic pyruvic transaminase and alkaline phosphatase, liver and bone metastases).

RESULTS

Patients, response and survival

Of the 148 patients entered, 75 were randomised to the CDE and 73 to the CDE/VIMP arms. One of the inclusion criteria was extensive disease, and 5 patients were considered ineligible because they had only limited disease. These patients were not used in the final analysis. Patient characteristics are shown in Table 1. The characteristics evaluated are comparable between both groups. The number of chemotherapy cycles is shown in Table 2. Only approximately 67% of the patients completed the treatment that they had been allocated to. The best response achieved is shown in Table 3. The major response rate was 68% and 70% in the standard and alternating arms, respectively. Early death due to toxicity was slightly higher in the standard treatment arm.

Table 2. Number of chemotherapy cycles by treatment arm

	Standard treatment Number of patients	Alternating treatment Number of patients
0–2	18	13
3	4	2
4	2	6
5	49	49

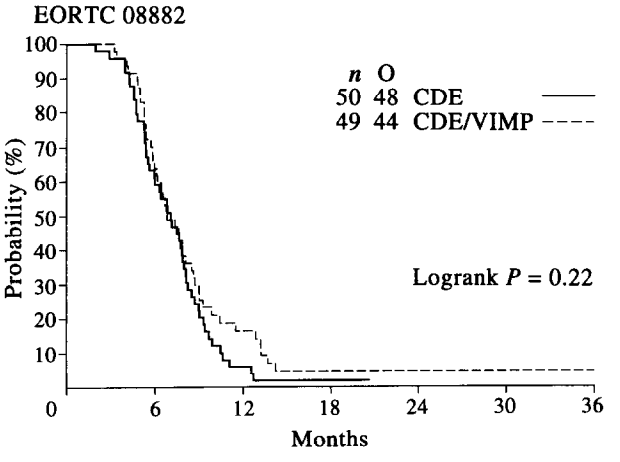

Figure 1. Duration of response, Kaplan–Meier curve. Logrank $P = 0.22$.

Overall, the response was more or less comparable. Response duration and time to progression in both treatment arms are shown in Figures 1 and 2. Survival curves are shown in Figure 3. There were no statistically significant differences between the standard and the alternating chemotherapy arms. Median survival was 7.6 months in the standard arm, 8.7 months in the alternating arm ($P = 0.243$). Median time to progression was 5.8 and 6.4 months, respectively ($P = 0.166$).

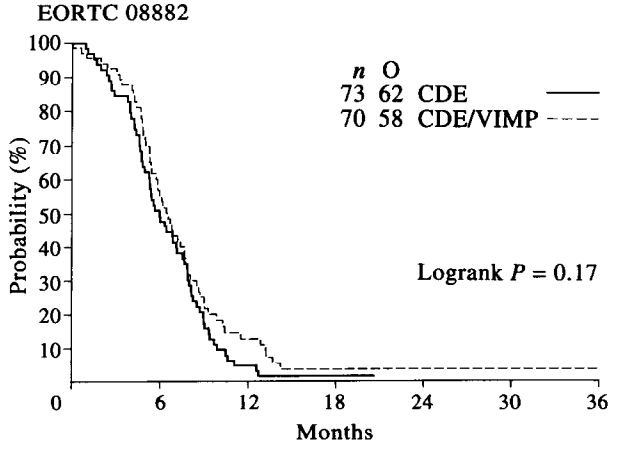

Figure 2. Time to progression, Kaplan–Meier curve. Logrank $P = 0.17$.

Table 3. Response to treatment for all eligible patients

	Standard treatment Number of patients (%)	Alternating treatment Number of patients (%)
Complete response (CR)	10 (14)	14 (19)
Partial response (PR)	40 (55)	35 (50)
CR + PR	50 (68)	49 (70)
No change	9 (12)	6 (9)
Progression	3 (4)	2 (3)
Early death--malignant disease	2 (3)	1 (1)
Early death-toxicity*	5 (7)	3 (4)
Early death--other cause	2 (3)	2 (3)
Not assessable	2 (3)	7 (8)

* All patients died of infection during the time of the nadir of the chemotherapy.

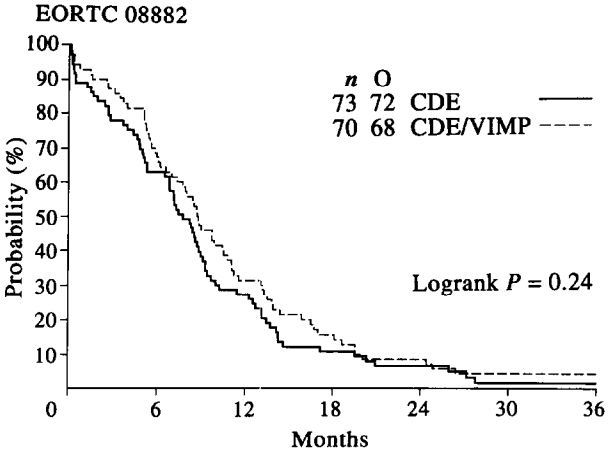

Figure 3. Duration of survival, Kaplan–Meier curve. Logrank $P = 0.24$.

Median response duration was 7.0 and 6.8 months, respectively ($P = 0.221$).

Toxicity

Haematological side-effects are shown in Table 4. Of the evaluable patients, 69% and 93% in the standard and alternating arms, respectively had grade 3–4 haematological toxicity ($P < 0.001$). Dose reduction was necessary in 33% of the patients, mostly for haematological toxicity. Dose intensities for all drugs in both arms were similar, as shown in Table 5. Treatment delay was seen in 27% of patients treated with CDE and 26% of those treated with alternating chemotherapy. Grade 3 and 4 infections were seen in 14% of the patients treated with CDE and in 17% of the patients treated with the alternating regimen. Of these, the main cause was haematological toxicity. Other side-effects were relatively mild (Table 6).

Table 4. Percentage of patients with haematological side-effects

	Standard treatment		Alternating treatment	
WHO toxicity	Grade 3	Grade 4	Grade 3	Grade 4
White blood cells	27	39	34	56
Platelets	10	5	15	29
Haemoglobin	7	1	20	3

Table 5. Percentage of drug actually given relative to the total theoretical dose

Drug	Alternating treatment ($n = 72$) Median (minimum–maximum)	Sequential treatment ($n = 69$) Median (minimum–maximum)
Cyclophosphamide	94 (20–106)	98 (20–105)
Doxorubicin	90 (0–118)	95 (21–111)
Etoposide	94 (7–125)	88 (20–117)
Vincristine		100 (0–200)
Ifosfamide		98 (0–142)
Mesna		97 (0–145)
Carboplatin		99 (0–138)

Table 6. Percentage of patients with non-haematological side-effects

Side-effect	Standard treatment Grade 3/4	Alternating treatment Grade 3/4
Cardiac	3	0
Stomatitis	6	3
Nausea/vomiting	13	18
Neurological	4	6

Multivariate analysis

After adjustment for possible prognostic factors (age, albumin levels, gender, performance status, levels of SGOT, SGPT and alkaline phosphatase, liver and bone metastases) using the Cox model, the treatment effect on survival was still not significant. Only gender (females versus males) and SGPT (WHO 0 versus 1–4) were retained in the final multivariate model at the 5% level of significance. No interaction between these two variables or between the treatment and either of these two variables was found to be significant. Relative to females, males had a relative risk (RR) of 1.8 (95% confidence interval (CI): 1.1–2.9, $P = 0.014$), and relative to patients with normal levels of SGPT, those with abnormal levels had a RR of 1.9 (95% CI: 1.3–2.8, $P = 0.001$).

DISCUSSION

Alternating chemotherapy for SCLC has been evaluated in clinical trials since 1979 [10]. In a review by Elliot and

colleagues in 1984, all controlled trials performed at that time had failed to show any consistent benefit for patients treated with alternating regimens [11]. In their conclusion, it was suggested that the time at which alternate cycles of treatment were introduced might be of critical importance. A study in which alternating chemotherapy was preceded by an initial period of induction chemotherapy showed no improvement in response duration [12]. These results were in contrast to data from the Finsen group demonstrating a prolonged duration of remission after alternating chemotherapy [13]. Furthermore, in future trials, confounding variables such as radiotherapy should be eliminated.

Since 1984, several large controlled trials have focused on alternating chemotherapy. These trials have varied extensively with regard to both the regimens tested and the patients (localised disease (LD), ED or both groups) included. In some studies, the chemotherapeutic regimen used in the control arm differed from the regimens used in the alternating arm completely [14] or just in detail [15]. Another factor complicating the interpretation of the results, primarily response duration and survival, was the use of maintenance chemotherapy in some studies [16]. Radiotherapy of the primary tumour was only used in patients with LD and, in some studies, only after completion of the chemotherapy [14, 15] or only in responding patients [17].

In the first, large, randomised trial, Evans and colleagues [18] treated 289 patients with ED with cyclophosphamide, doxorubicin and vincristine (CAV) or CAV alternating with cisplatin and etoposide (PE). Patients receiving alternating chemotherapy demonstrated significantly better response rates, progression-free survival and overall survival rates compared with patients treated with CAV. However, if patients with locoregional disease were excluded from the analysis, and sex and performance score were taken into account, overall survival was no longer statistically significant, though time to progression was. In two further large, randomised trials [19, 20] CAV and PE were compared with alternation of these regimens (CAV/PE). Both studies differed in the dosages and the time scheduling of the drugs, and in one, both patients with LD and those with ED (288 evaluable patients) were included, while in the other, the patients (437 eligible patients) all had ED. In the latter study, no significant differences in treatment outcome for CAV, PE and CAV/PE could be demonstrated. Overall response rates were 51%, 61% and 59% and complete response (CR) rates were 7%, 10% and 7%, respectively. Median survival times were 8.3, 8.6 and 8.1 months, respectively, with a (statistically non-significant) trend towards a longer median time to progression in the alternating arm. In the study by Fukuoka and colleagues, response rates for PE (78%) and CAV/PE (76%) were significantly higher than for CAV (55%), albeit the CR rates were similar for the three groups [19].

Wolf and colleagues [21] compared alternating chemotherapy (ifosfamide/etoposide (IE) and CAV) with response-oriented chemotherapy (IE) for a maximum of six cycles in a multicentre randomised trial with 321 patients (LD and ED). In the response-oriented arm, patients were treated with IE to a maximal response and were subsequently switched to CAV. Patients with stable disease (SD), after only one cycle, were also given CAV in the next cycle. In the alternating treatment arm, patients were shifted to second-line treatment only if progression occurred. Patients with LD received chest radiotherapy following chemotherapy. Overall response rates were 77% and 70% for the alternating and response-oriented arm, respectively. The CR rate was 26% in both arms. Median survival times were 9.7 and 10.7 months, and 2-year survival rates were 11% and 9% for the alternating and response-oriented groups, respectively. The study did not demonstrate any advantages for alternating chemotherapy over the response-oriented treatment.

The concept of alternating non-cross-resistant chemotherapy has been proved in the laboratory situation to be an effective treatment for experimental tumours. However, applying this experimental approach to a clinical situation is rather difficult. Firstly, one has to try to define what is non-cross-resistant in the clinical situation and secondly one has to show that the treatments which are supposed to be non-cross-resistant are equally effective. This has been tested by the EORTC LCCG in two previous studies. In the first study, the carboplatin–ifosfamide combination was equipotent with the standard CDE regimen [4]. In the second study, the carboplatin–ifosfamide combination was effective in $> 50\%$ of patients with clinical resistance to CDE, and the CDE regimen was effective in $\geq 50\%$ of patients initially treated with a carboplatin-containing regimen [5]. If these results are compared with the frequently used CAV/EP combination, it is questionable whether CAV and EP are equipotent. In two studies, EP was superior to CAV [17, 19], but in two others efficacy was similar [20, 22].

The non-cross-resistance of CAV and EP was examined in a number of initially responding patients in the randomised studies. The response rate of EP after CAV was 28%, whereas only 14% responded to CAV after EP [20]. Of the initially non-responding patients, 15% [20] and 23% [19] responded to EP, while only 8% [19, 20] responded to CAV after proven resistance to EP. One may therefore conclude that the frequently used CAV/EP regimen is not the appropriate combination for evaluating the Goldie–Coldman hypothesis in SCLC. Testing the equipotent regimens CDE and VIMP, with a clinically proven degree of non-crossresistance ($\geq 50\%$), is probably the best achievable analogy of the laboratory model. Whether this would result in a clinically significant improvement has been tested in this study. Unfortunately, accrual for our study suffered from other competing studies and was stopped before reaching the planned number of patients. The number of patients needed to find a clinically significant difference in median survival of 3 months was 180 per treatment arm. Taking into account the median survival of 7.6 months in the standard arm, the observed number of deaths (145 out of 148 randomised patients) would have been enough to detect an increase in the median survival in the alternating arm to 9.2 months with a power of 80%. In other words, we can conclude that such an increase in the median survival could not be reached with the alternating regimen.

Even if this minimal difference had been reached in the present study, the clinicians would still not have considered the trial to be worthwhile, and the concept of alternating chemotherapy for SCLC with drugs that are currently available has to be rejected. Until new drugs with clinically proven non-cross-resistance are available, further testing of this concept is not necessary.

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