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Comparison of Two Carboplatin-containing Regimens with Standard Chemotherapy for Small Cell Lung Cancer in a Randomised Phase II Study

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The EORTC Lung Cancer Cooperative group performed a randomised phase II study in patients with small cell lung cancer comparing the standard cyclophosphamide/doxorubicin/etoposide (CDE) regimen with two regimens containing the new and active cisplatin derivative, carboplatin, 400 mg/m² in combination with ifosfamide, a drug without important myelotoxicity, at a dose of 5 g/m² (IMP) or the non-myelotoxic drug vincristine twice 2 mg (VP). Of 178 evaluable patients, 63 received CDE [30 limited disease (LD), 33 extensive disease (ED)], 55 received IMP (22 LD, 33 ED) and 60 (26 LD, 34 ED) were treated with VP. The response duration was not statistically different: CDE 31 weeks, IMP 29 weeks and VP 21 weeks. The time to progression after CDE was 28 weeks, IMP 24 weeks and VP 17 weeks. This was significantly shorter after VP than after CDE ($P = 0.017$). The 60% response rate of the VP combination was low compared with CDE (83%) and IMP (77%). Toxicity of all three regimens was acceptable, and dose reduction for myelosuppression was necessary in only a minority of the patients. We conclude from this study that the combination of carboplatin, at the maximally tolerated dose of 400 mg/m², in combination with ifosfamide 5 g/m², is an active regimen with efficacy comparable with the standard CDE regimen.
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INTRODUCTION

AFTER THE introduction of chemotherapy for small cell lung cancer (SCLC) more than two decades ago, the initially impressive results [1] have unfortunately not resulted in a cure for many patients. The results of (chemo)therapy have reached a plateau in the last 10 years. One way to progress from this is the introduction of new active agents into existing treatment protocols.

One of the most promising agents in phase I and II studies is the cisplatin derivative carboplatin [2, 3]. Its 60% response rate in previously untreated extensive disease patients is high [2]. Compared to cisplatin it is less nephro, oto and neurotoxic and also less emetogenic. Dose limiting toxicity was myelosuppression, especially thrombocytopenia, at a dose of 400 mg/m² in a 4-weekly schedule [4]. If combined at this dose with the myelotoxic drug teniposide unacceptable myelotoxicity was seen [5].

In order to incorporate carboplatin in combination chemotherapy regimens at the maximum tolerated dose (400 mg/m²),

Table 1. Patients' characteristics (n = 178)

	CDE	IMP	VP
n (M/F)	63 (49/14)	55 (46/9)	60 (47/13)
Median age (range)	59 (39–70)	59 (38–69)	57 (39–70)
LD/ED	30/33	22/33	26/34
Performance score (ECOG)			
0–1	48	43	47
2	10	8	8
3	5	4	5

it needs to be combined with active drugs without significant myelosuppression. Ifosfamide [6] and vincristine are suitable candidates for this purpose.

In this randomised phase II study we compared the efficacy of carboplatin and ifosfamide (IMP), and carboplatin and vincristine (VP), with the standard regimen of the EORTC Lung Cancer Cooperative Group cyclophosphamide, doxorubicin and etoposide (CDE) [7].

PATIENTS AND METHODS

Patients

From April 1986 until June 1987, 185 newly diagnosed patients with histologically or cytologically proven SCLC were entered in this multicentre study. Patient characteristics and staging are shown in Table 1. Eligibility criteria were: no previous chemotherapy, normal renal function (creatinine clearance > 60 ml/min), normal bilirubin (< 25 μmol/l), ECOG performance score ≤ 3, age ≤ 70 years, normal number of leucocytes (> 3.0 × 10^9/l) and platelets (> 100 × 10^9/l). In case of bone marrow metastases all values of leucocytes and platelets were acceptable. Informed consent was obtained from all patients.

Staging

All patients underwent routine staging procedures including physical examination, chest X-ray, standard or computed tomography (CT) of the chest, bronchoscopy, ultrasound or CT of the abdomen, isotope bone scans, neurological examination, bone marrow biopsy, routine full blood cell count, serum electrolytes, liver and renal function tests. Patients with disease limited to one hemithorax and mediastinal and supraclavicular nodes were considered to have limited disease (LD), all other patients had extensive disease (ED). Restaging included all initially abnormal investigations, in case of a radiological complete response bronchoscopy was also repeated.

Therapy

All patients were stratified for performance score (PS), disease extent and institution, and randomised to one of the three treatment arms.

Treatment 1 (*CDE*). This consisted of cyclophosphamide 1 g/m² intravenously on day 1, doxorubicin 45 mg/m² intravenously on day 1, and etoposide 100 mg/m² intravenously days 1, 3 and 5. Maximally five courses were given at 3-week interval between the courses.

Treatment 2 (*IMP*). This consisted of carboplatin 400 mg/m², dissolved in 250 ml dextrose 5% and given as a 30 min intravenous infusion, and ifosfamide 5 g/m², given as a 24-h infusion. Mesna 0.6 g/m², was given as an intravenous bolus with 200 ml mannitol (20%) before the ifosfamide infusion. During the ifosfamide infusion and the following 12 h 3.75 g/m² mesna was given as a continuous infusion. Forced diuresis was established by giving 6 l of dextrose/saline in 38 h. Maximally, five courses were given at 4-week interval.

Treatment 3 (*VP*). This consisted of carboplatin, given in the same way as described above, and vincristine 2 mg intravenous bolus on day 1 and 8. Maximally five courses were given at 4-week interval.

Patients with progression went off study and were treated according to the opinion of the responsible physician. Most patients relapsing after the carboplatin containing regimens received CDE. Patients with a complete response after chemotherapy received prophylactic cranial irradiation 12 × 2.5 Gy. Thoracic irradiation was not allowed before patients went off study for tumour progression.

Response and toxicity

Response was evaluated after two and five courses. Tumour response was defined according to standard criteria: complete response (CR) was defined as the disappearance of all known disease for at least 4 weeks; partial response (PR) was defined as a reduction in the product of the greatest tumour diameter and of its perpendicular of all measurable lesions by at least 50% for at least 4 weeks; stable disease (SD) was defined as a decrease of < 50% or an increase of < 25% in the size of one or more lesions. Progressive disease (PD) was defined as an increase of > 25% in tumour size or the occurrence of any new lesions including brain metastases. Response duration and survival were measured from the start of treatment to progression. Toxicity was graded according to standard WHO criteria [7].

Statistics

Response duration, progression-free survival and survival curves were estimated by the Kaplan–Meyer method and tested for significance using the Mantel–Haenszel technique.

RESULTS

Patients, response and survival

Of 185 patients entered, 7 were not eligible and 9 not evaluable for response. Reasons for not being eligible were: non-SCLC (*n* = 2), over 70 years of age (*n* = 2), active infection (*n* = 1), second malignancy (*n* = 1) and informed consent not obtained

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Table 2. Best response to induction therapy

	CDE	IMP	VP
n	60	51	58
CR	15 (25)	6 (12)	8 (14)
PR	35 (58)	33 (65)	27 (47)
NC	4 (7)	2 (4)	5 (9)
PD	4 (7)	7 (14)	16 (28)
ED*	2 (3)	3 (6)	2 (3)

No. (%).
CR = complete response, PR = partial response, NC = no change, PD = progressive disease, *ED = early death, within 3 weeks from the start of therapy.

(n = 1). Reasons for not being evaluable for response were: treatment never started (n = 3), tumour non-evaluable (n = 1), excessive toxicity (n = 2) and patient refusal (n = 3). Toxicity was not evaluable in the "treatment never started" patients and in 4 patients of whom data were missing. The characteristics of the evaluable patients are shown in Table 1. The best response achieved during the induction therapy is shown in Table 2. The overall response rate (CR + PR) was 83% in the CDE arm, 77% in the IMP arm and 60% in the VP arm.

Response duration and time to progression of the three different groups are shown in Figs 1 and 2. The duration of response of the three arms was not statistically different: CDE versus IMP, P = 0.845; CDE versus VP, P = 0.186; and IMP versus VP, P = 0.173. The time to progression after CDE and VP was statistically different (P = 0.017), whereas IMP versus VP and CDE versus IMP were not different (P = 0.103 and P = 0.494, respectively).

Survival curves of the three treatment arms are shown in Fig. 3. There was no statistically significant difference between CDE, IMP and VP. The median response duration, time to progression and survival are shown in Table 3.

Toxicity

The median number of courses given was five for CDE and IMP, and four in the VP arm. Myelosuppression was the most important toxicity in the CDE and IMP arm, and was rather mild in the VP arm (Table 4). Dose reduction was necessary in

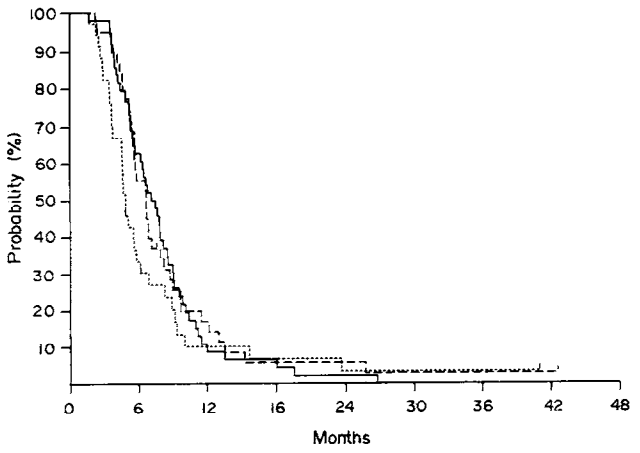

Fig. 1. Response duration: ——— = CDE, - - - - = IMP, ... = VP.

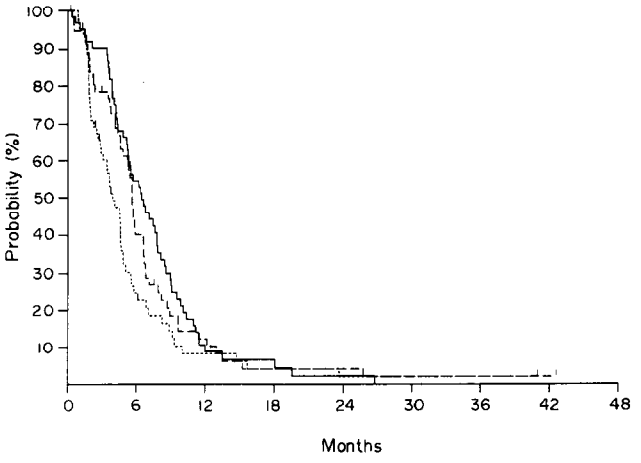

Fig. 2. Time to progression: ——— = CDE, - - - - = IMP, ... = VP.

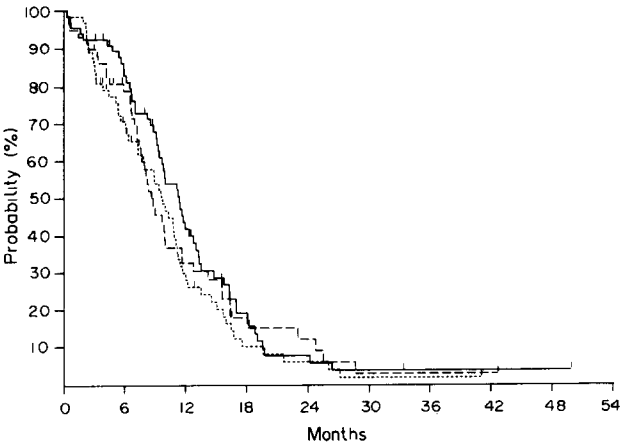

Fig. 3. Survival: ——— = CDE, - - - - = IMP, ... = VP.

Table 3. Median response duration, time to progression and survival

	CDE	IMP	VP
Response duration	31 (0–116)	29 (0–185)	21 (0–178)
Time to progression	28 (0–116)	24 (0–185)	17 (0–178)
Survival	49 (1–244)	37 (1–185)	42 (2–178)

Weeks (range).

Table 4. Haematological side-effects

Therapy	No. of courses	Leucocytopenia (%)		Thrombocytopenia (%)	
		Grade 3	Grade 4	Grade 3	Grade 4
CDE	267	25	16	15	2
IMP	217	35	17	40	10
VP	216	5	1	17	3

Table 5. Non-haematological side-effects

Side-effect	CDE	IMP	VP
Nausea/vomiting	79 (21)*	89 (30)	82 (12)
Alopecia	98 (60)	92 (51)	50 (4)
Infection	28 (10)†	25 (4)†	14 (5)†
Neurotoxicity	7	8	37 (4)
State of consciousness	–	6 (4)	–
Diarrhoea	7 (2)	13	11
Renal	3 (2)	4	–
Haematuria	–	8	–

Percentage of courses.
* Grade 3/4 toxicity is given in parentheses.
† Of these 3%, 1% and 3%, respectively, were aplasia-related.

19% of the CDE courses, in 13% of the IMP courses and in only 3% of the VP courses; the dose of vincristine was reduced in 13% of the courses. In the CDE arm 93.8%, in the IMP arm 95.2% and in the VP arm 98.7% of the planned dose of chemotherapy had actually been given. Of the CDE courses 17 were delayed 1 week and six ≥ 2 weeks. For IMP this was 10 and 6, and VP 3 and 3, respectively.

Other toxicities are shown in Table 5. Alopecia was strikingly less common in the VP arm, whereas peripheral neurotoxicity occurred much more often in this arm. In 2 patients, severe central nervous system toxicity due to ifosfamide was seen; in both patients it was reversible within a few days. These patients were not retreated with ifosfamide.

DISCUSSION

In this phase II study it was shown that it is possible to combine carboplatin at the maximum tolerated dose of 400 mg/m^2 with a drug without significant myelotoxicity.

Myelotoxicity of both carboplatin-containing regimens was acceptable and other side-effects were not significantly different from the "standard" CDE regimen. The antitumour results obtained with the carboplatin–vincristine combination are inferior to the CDE regimen. The response rate was lower and the time to progression was significantly shorter. Combining carboplatin at this dose with a much more active drug as isosfamide resulted in a response rate, response duration and time to progression comparable to CDE. Overall survival in the three groups was not different. This may be due to second-line treatment in patients failing on both carboplatin-containing regimens. A similar result was seen in a previous EORTC study [7] in which short-term chemotherapy (five courses) was followed by a shorter response duration than "maintenance" chemotherapy. However, the survival in both groups did not show statistical difference. Retreatment of patients relapsing after five cycles resulted in a significant response [9] and this may have had impact on survival.

It is not possible to conclude from this study that carboplatin is the ideal substitute for cisplatin in first-line therapy for SCLC. It has certain toxicity advantages over cisplatin and it is much easier to handle. In this study there were no signs of clinically relevant renal function disturbances measured by serum creatinine, although with more sophisticated techniques it was shown that at the carboplatin dose of 400 mg/m^2 glomerular filtration rate and effective renal plasma flow decreased significantly [10]. Improvement in the results of combination chemotherapy with much higher doses of carboplatin, without encountering the nephrotoxic side-effects known from the parent compound, is therefore not realistic [11]. Another approach to improve the results of carboplatin-based first-line chemotherapy is increasing the number of drugs in the induction regimen. At least three such studies have been reported, in all of which one or two drugs were added to the combination of carboplatin and etoposide [12–14]; overall the results were certainly comparable with the "standard" regimens for SCLC. Considerable myelotoxicity was encountered if carboplatin was administered at the maximally tolerated dose of 400 mg/m^2 [13]. Two possible methods to reduce this side-effect are the individual dosing of carboplatin [15], or the application of haematopoietic growth factors, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) [16].

A potential application of carboplatin is in a second-line regimen. The cisplatin–etoposide combination [17, 18] is generally considered the most active regimen in relapsing patients. However, in these patients, in whom palliation is the main goal of therapy, side-effects should be minimal and application of such a toxic regimen is questionable.

The response rate of 19% in a small group of relapsing patients may be promising [2, 19]. In a group of patients with early progression after chemotherapy the combination of carboplatin and vincristine resulted in a 36% partial response rate [20]. Ifosfamide is also active in patients with early tumour progression [21]. Adding this drug to the carboplatin–vincristine combination resulted in 10 out of 19 (53%) responses in a comparable group of patients. However, myelotoxicity was severe [22]. Based on these studies, the EORTC Lung Cancer Cooperative Group will evaluate a carboplatin-based regimen in an alternating schedule with the standard CDE regimen.

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Cyclic Alternating Chemotherapy of High-grade Malignant Non-Hodgkin Lymphomas with VIM-Bleo and CHOP

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Between 1986 and 1988, 81 patients with high grade malignant non-Hodgkin lymphoma according to the Kiel classification were treated with the VIM-Bleo/CHOP-regimen: etoposide 100 mg/m² intravenously on days 1–3, ifosfamide 1.5 g/m² intravenously days 1–5 with mesna for prophylaxis of cystitis, methotrexate 30 mg/m² intravenously on days 3, bleomycin 10 mg intravenously on days 8 and 15, cyclophosphamide 750 mg/m² day 22, doxorubicin 50 mg/m² day 22, vincristine 1.4 mg/m² on day 22, and prednisolone 100 mg postoperatively on days 1–5 and 22–26. Cycles were repeated four times beginning on day 43. Regions with bulky disease were irradiated after chemotherapy. 36 patients (44%) had stage II, 12 (15%) stage III and 33 (41%) stage IV disease. B-symptoms were present in 49% of patients. Serum lactate dehydrogenase activity was elevated in 53%. Overall, 59 patients (73%) achieved a complete and 14 (17%) a partial remission. 8 (9%) had stable or progressive disease. After a median follow up of 30 months thus far, probability of long-term relapse free survival is 66% for patients in complete remission. Overall survival is 72% at 24 months. Toxicity from treatment was very low with leukopenia being the main side effect. Major infections were observed in only 2% of cycles with one treatment related death. VIM-Bleo/CHOP is a well tolerated regimen with remission rates in the range of other, more toxic regimens. However, cyclic alternating treatment did not improve results as compared with repeated treatment with a single standard protocol.
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INTRODUCTION

DURING THE past 10 years, several aggressive chemotherapy protocols for high and intermediate grade malignant non-Hodgkin lymphomas have been published [1–6]. By adding further drugs, i.e. bleomycin, etoposide or high-dose methotrexate, to the standard CHOP protocol [7], by introducing other treatment regimens for consolidation therapy or by reducing treatment intervals, treatment results were reported to improve significantly. Complete remissions could be achieved in up to 87% of patients [6], with long term survival ranges between 50 and 70%. However, most studies were single institution projects. Results with the same protocol were significantly worse when used in other institutions or larger study groups [8–10]. Randomised studies comparing the newer regimens have been initiated [9, 11], but results are published only in one [11]. Therefore, it is not clear, which of the newer protocols is optimal. It is even unclear, whether any are truly superior to the CHOP protocol [9, 10, 12].

In an attempt to improve treatment results in high grade malignant non-Hodgkin lymphoma, we treated patients with a cyclic alternating regimen named VIM-Bleo/CHOP. This regimen was based on published reports [13] as well as our own