containing combination chemotherapy, which usually yielded response rates of around 20% [1, 2, 5, 6]. Two of the 7 responses in our study, however, were obtained in patients with locally advanced disease who were in fact not eligible. Of 30 patients with metastatic cancer, 5 responded (response rate 17%; 95% confidence intervals 9–39%). Cisplatin, therefore, can be considered a modestly active drug in advanced pancreatic carcinoma and a further search for combinations with other active agents appears reasonable. Continuous infusion (CI) of 5-FU has gained a renewed interest, especially in the treatment of advanced colorectal cancer and is also of potential interest in pancreatic cancer. A phase II study of cisplatin, 100 mg/m^2 every 4 weeks, combined with CI of 5-FU, days 1–5, yielded a 27% response rate in 38 patients [5]. Another study, in which protracted CI of 5-FU was combined with weekly cisplatin, 20 mg/m^2, yielded a 16% response rate [6].

Another possible approach is the combination of active cytotoxic drugs with biological agents such as interferons, because synergism with these agents has been observed *in vitro* and *in vivo* [7, 8]. Therefore, our group is now planning to assess the combination of cisplatin with alpha-interferon.

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Acknowledgements—Other investigators who contributed patients in this study were:
M. Gignoux, CHU, Caen, France; M. Buset, Hopital Erasme and Hopital Brugmann, Brussels, Belgium; M. Fickers, De Wever Hospital, Heerlen, The Netherlands; E. Francois, Centre Antoine Lacassagne, Nice, France; A. de Graeff, Academic Hospital Utrecht, The Netherlands.

Eur J Cancer, Vol. 29A, No. 2, pp. 204–207, 1993.
Printed in Great Britain

0964–1947/93 $5.00 + 0.00

Testing the Possible Non-cross Resistance of Two Equipotent Combination Chemotherapy Regimens Against Small-cell Lung Cancer: A Phase II Study of the EORTC Lung Cancer Cooperative Group

Pieter E. Postmus, Egbert F. Smit, Anne Kirkpatrick and Ted A.W. Splinter

The Goldie–Coldman hypothesis of alternating non-cross resistant combination chemotherapy regimens for small-cell lung cancer has never been adequately evaluated. In previously reported studies non-cross resistance and/or equipotency of the combinations used had not been tested before the phase III study was started. We describe two combination chemotherapy regimens with comparable efficacy against small-cell lung cancer and present a phase II test of their possible non-cross resistance. Patients clinically resistant to cyclophosphamide, doxorubicin and etoposide (CDE), were treated with the second-line regimen consisting of vincristine, ifosfamide, mesna and carboplatin (VIMP) (n = 25). This resulted in 1 complete and 14 partial responses, response rate 60% [95% confidence interval (CI): 38.7–78.9%]. Patients clinically resistant to vincristine, carboplatin (n = 22) or ifosfamide, mesna, carboplatin (n = 21) were treated with CDE, resulting in 6 complete responses and 16 partial responses, response rate 51% (95% CI: 35.5–66.7%). The clinical value of such a degree of non-cross resistance has to be evaluated in a phase III study.
Eur J Cancer, Vol. 29A, No. 2, pp. 204–207, 1993.

INTRODUCTION

SMALL-CELL LUNG CANCER (SCLC) is a chemotherapy-sensitive tumour with response rates of 80–90% in most studies evaluating combination chemotherapy regimens. Despite this initially impressive result, the number of patients with long-term disease-free survival is less than 10%. One of the reasons for this is existence of chemotherapy-resistant cell clones, either present from the start of treatment, or emerging during treatment. Evidence for emerging heterogeneity and resistance can be found in clinical investigations as well as from cell lines and heterotransplanted tumours.

Goldie and Coldman have proposed a simple mathematical model of the probability of the development of resistant cell clones within a tumour [1]. This model assumes that tumours

grow exponentially and each course of chemotherapy results in log cell-kill. The outcomes of two treatment strategies, alternation of two non-cross-resistant drugs and sequential administration of therapy, were 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 sequential therapy. Although it is impossible to prove whether these two assumptions concerning the tumour are correct, the clinical experience with Hodgkin's disease [2] makes it worthwhile to test the Goldie–Coldman hypothesis in SCLC. Two conditions have to be fulfilled before we can clinically test the Goldie–Coldman hypothesis: (1) the two combination chemotherapy regimens have to be equipotent with regard to tumour cell-kill, i.e. comparable response rates; (2) there has to be non-cross resistance between these two regimens. This means that a reasonable number of patients progressing during the induction regimen A have to respond to regimen B. The same is true for patients treated with the induction regimen B who, in case of progression, must respond to regimen A [3].

In this study, two equipotent regimens, as was shown in a recent previous study [4], were evaluated for their degree of non-cross resistance in two parallel phase II studies.

PATIENTS AND METHODS

Patients

From June 1986 until May 1990, 68 patients were entered in this study. Eligibility criteria were: histologically or cytologically proven SCLC, age $\leq$ 75 years, ECOG performance status $\leq$ 3, normal serum creatinine ($<$ 125 μmol/l), normal serum bilirubin ($<$ 25 mmol/l), normal leukocytes ($\geq 3.0 \times 10^9$/l) and platelets ($\geq 100 \times 10^9$/l), no signs of central nervous system metastases, documented tumour progression during or within 3 months after the last chemotherapy. All patients had previously been treated for SCLC with combination chemotherapy regimens according to EORTC protocol 08862 [4] as described in the therapy section. The study was approved by the medical ethical committees of the participating institutes. All patients gave oral informed consent.

Staging

All patients had undergone routine staging procedures prior to first-line therapy at the time SCLC was diagnosed, which consisted of physical examination, chest roentgenogram, standard or computer tomography (CT) of the chest, bronchoscopy, ultrasound or CT of the abdomen, neurological investigation, bone marrow biopsy, routine blood cell counts, serum electrolytes and 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). At the time of tumour progression after first-line therapy, investigations for measuring tumour response after the second-line chemotherapy regimens were performed. In case of a possible complete response (CR) after second-line therapy, bronchoscopy and all other initially abnormal investigations, i.e. before the start of first-line therapy, were also repeated.

Therapy

Patients were initially treated with one of three combination chemotherapy regimens, with randomisation being performed according to standard procedures of the EORTC.

Treatment 1 (CDE) consisted of cyclophosphamide 1 g/m^2 intravenously day 1, doxorubicin 45 mg/m^2 intravenously day 1, and etoposide 100 mg/m^2 intravenously days 1, 3 and 5. Maximally, five courses were given with 3-week intervals between the courses.

Treatment 2 (IMP) consisted of carboplatin 400 mg/m^2, dissolved in 250 ml dextrose 5% and given as a 30-min infusion, and ifosfamide 5 g/m^2, given as a 24-h infusion. Mesna, 0.6 g/m^2, 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/m^2 mesna was given as a continuous infusion. Forced diuresis was established by giving 6 l dextrose/saline in 38 h. Maximally, five courses were given with 4-week intervals between the courses.

Treatment 3 (VP) consisted of carboplatin, given as described previously, and vincristine 2 mg intravenous bolus on days 1 and 8. Also, a maximum of five courses were given with 4-week intervals between the courses. In the case of tumour progression during or within 3 months after the end of therapy, patients initially treated with treatment 2 (IMP) or 3 (VP) received CDE.

Patients progressing on CDE received VIMP (IMP combined with vincristine 2 mg intravenous bolus on days 1 and 8). Treatment was continued for a maximum of five courses if patients responded or remained stable. All patients who had tumour progression more than 3 months after the last chemotherapy were retreated with the first-line therapy; in case of progression during re-induction, the previously described therapy was started. Patients with progression went off study and were treated according to the opinion of the responsible physician and were followed for survival.

Response and toxicity

Response was evaluated after each course by measuring the target lesion defined before the start of second-line therapy. Tumour response was defined according to standard WHO criteria. Response duration was measured from the start of second-line treatment to progression. Survival was measured from the start of second-line therapy. Toxicity was graded according to standard WHO criteria [5] and scored on day 14 of each course.

RESULTS

Patients

Patient characteristics are listed in Table 1. 22 patients who were initially treated with VP were treated with CDE at progression, 21 patients initially treated with IMP also received CDE, and 25 patients who had been treated with CDE and were treated with VIMP at relapse.

Response and survival (Tables 2, 3)

Of the patients initially treated with VP or IMP, 6 had a CR and 16 had a partial response (PR) after CDE, response rate 51% [95% confidence interval (CI): 35.5–66.7%]. VIMP resulted in 1 CR and 14 PR, total response rate 60% (95% CI: 38.7–78.9%). Response duration was 19 weeks (median, range 12–34) after CDE and 16 weeks (median, range 4–30) after

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Revised 12 July 1992; accepted 17 July 1992.

Table 1. Patients' characteristics

	First line therapy		
	IMP	VP	CDE
No. of patients	6 F/15 M	3 F/19 M	3 F/22 M
Age (range)	57 (38–69)	58 (39–73)	55 (43–67)
PS 0	5	4	5
1	9	10	10
2	5	7	5
3	2	1	5
LD/ED	6/15	10/12	10/15
No. of patients treated with no. of cycles			
1st line 1	0	2	0
2	3	7	2
3	2	3	0
4	1	3	4
5	15	7	13
> 5	0	0	6
Interval between 1st line and 2nd line (weeks)			
0– 4	8	14	11
5– 8	6	7	7
9–13	7	1	7

IMP = Ifosfamide, mesna and carboplatin; VP = carboplatin and vincristine; CDE = cyclophosphamide, doxorubicin and etoposide; PS = performance status; LD = limited disease; ED = extensive disease; M = male; F = female.

Table 2. Response to first-line and second-line therapy

			Response to second-line VIMP					
		CR	PR	SD	PD	TD/NE	TOTAL	
			1	14*	2	6	2	25
Response to first-line CDE	CR	5	1	3	—	—	1	
	PR	15	—	9*	2	3	1*	
	SD	3	—	—	—	3	—	
	PD	2	—	2	—	—	—	
	Total	25	—	—	—	—	—	

*1 patient died after two courses of toxicity.
Numbers within the rectangle show responses of individual patients to both treatments.

Table 3. Response to first-line and second-line therapy

			Response to second-line CDE					
			CR	PR	SD	PD	TD/NE	Total
			6	16	8	10	3	43
Response to first-line VP/IMP	CR	2	1	1	—	—	—	
	PR	23	1	11	3	6	2	
	SD	3	—	1	2	—	—	
	PD	15	4	3	3	4	1	
	Total	43	—	—	—	—	—	

Numbers within the rectangle show responses of individual patients to both treatments.

VIMP. The response rate after CDE given to patients initially treated with VP was different despite the higher number of LD patients and the lower number of chemotherapy courses before CDE was started. Survival from the start of second-line chemotherapy was 22 weeks for patients treated with CDE (median, range 1–83) and 19 weeks for patients treated with VIMP (median, range 2–117). Responding patients had a median survival of 24 weeks (range 4–83) after CDE and a median survival of 21 weeks (range 6–64) after VIMP. In non-responders the median survival after CDE was 11 weeks (range 2–32) and 12 weeks (range 2–117) following VIMP.

Toxicity

Myelosuppression was the most important side-effect. In the group treated with CDE 125 courses were given. During 26 courses (21%) dose reduction was necessary owing to myelotoxicity. In 38% of the evaluable courses (n = 125) grade 3 and in 25% grade 4 leukocytopenia was seen, and in 6 and 3% grades 3 and 4 thrombocytopenia respectively were also noted.

In the group treated with VIMP 65 courses were given. Dose reduction was necessary in 17 courses (26%) owing to myelotoxicity. In 26 and 40% of the evaluable courses (n = 65) grades 3 and 4 leukocytopenia were respectively seen, and grades 3 and 4 thrombocytopenia were noted in 8 and 45%, respectively.

Other side-effects, all ≤ grade 2, were nausea and vomiting, anaemia and neuropathy. All patients had alopecia before the start of second-line therapy.

DISCUSSION

The Goldie–Coldman hypothesis has attracted many investigators to test its clinical value mostly in large randomised studies. However, after at least 19 studies [6] over more than 10 years with more than 4000 patients, the clinical relevance of this hypothesis for SCLC remains unproven. All studies are subject to strong criticism since in none of these studies were the conditions for adequate evaluation of the hypothesis, as stated in the introduction, fulfilled. The treatments were selected without adequately testing their presumed non-cross resistance in properly designed phase II studies in well-defined chemotherapy-resistant patients [7]. An example of this is the large difference in response after the combination of cyclophosphamide, doxorubicin and vincristine (CAV) given to patients not responding during treatment with etoposide and cisplatin (EP), and the response after EP given to patients clinically resistant to CAV. After CAV only one responder out of 11 patients was seen whereas 6 out of 18 patients responded to EP [8]. This shows asymmetry between the two combinations. Moreover, the two combinations are probably not equipotent [9]. The results of so-called non-cross-resistant studies are furthermore confounded by the fact that the probability of a response after any second-line regimen is highly dependent on the time interval between first- and second-line treatments [10, 11].

In an earlier study CDE, VP and IMP were evaluated in previously untreated patients. There were no differences between CDE and IMP with regard to response rate, response duration and survival. The VP combination was less effective [4]. In a previous study the VP combination resulted in a 36% response rate in patients clinically resistant to CDE [12]. This showed some non-cross resistance between VP and CDE. Adding ifosfamide to the VP combination might have improved the potency of the combination [13].

In the reported study two different combinations, CDE and VIMP, were tested in patients with proven or very likely resistance to the induction chemotherapy initially given. With both regimens a > 50% response rate was seen. Unfortunately, most responses were only partial and short-lived. These results prove that there is a certain degree of non-cross resistance between the combinations used and confirm again the equipotency of the CDE and VIMP combinations. Whether this degree of non-cross resistance is large enough to improve the survival in comparison with the standard treatment CDE still has to be shown. Currently, the EORTC Lung Cancer Cooperative Group is performing a randomised study between CDE and alternating CDE and VIMP in patients with extensive SCLC.

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Acknowledgements—Other physicians participating in this study were: F J. van Breukelen, Mariastichting Haarlem, The Netherlands; J.Th.W. Burghouts, Grootziekengasthuis Den Bosch, The Netherlands; D.N. Carney, Mater Misericordia Hospital Dublin, Ireland; J. Festen, Radboud Ziekenhuis Nijmegen, The Netherlands; G. Giaccone, Ospedale San Giovanni Torino, Italy; M. Koolen, Academisch Medisch Centrum Amsterdam, The Netherlands; J.L. van de Lichte, Maria Ziekenhuis Tilburg, The Netherlands; G. Miech, Centre Hospitalier de Mulhouse, France; F.M.L.H.G. Palmen, St. Elizabeth Ziekenhuis Tilburg, The Netherlands; A. S. T. Planting, Daniël den Hoed Kliniek Rotterdam, The Netherlands; E. Quoix, CHR de Strasbourg, France; M. Rinaldi, Institute Regina Elena Roma, Italy; K. Roozendaal, Onze Lieve Vrouwe Gasthuis Amsterdam, The Netherlands; G. Scagliotti, University of Torino, Italy; C. Vendrik, University Hospital Utrecht, The Netherlands; N. van Zandwijk, Nederlands Kanker Instituut Amsterdam, The Netherlands.