Eur J Cancer Clin Oncol, Vol. 23, No. 8, pp. 1197–1205, 1987.
Printed in Great Britain

0277-5379/87$3.00+0.00

The Prognostic Value of Response to the First Cycle of Chemotherapy in Small Cell Lung Cancer. Results of a Multicenter German Trial

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Abstract—*The prognostic significance of evaluation of response according to chest X-ray after only one cycle of treatment was investigated in patients with small cell lung cancer (SCLC). Three hundred and six patients entered a multicenter randomized German trial testing alternating vs. sequential chemotherapy. Decrease of tumor size after the first cycle was seen to be 78% in the alternating group and 70% in the sequential group. Stable disease occurred in 25% of the sequentially treated and 19% of the alternatingly treated patients. No substantial differences in pretreatment characteristics were noticed between patients with stable disease in sequential and alternating treatment. In sequential therapy, median survival was 323 days for patients with decrease of tumor size after the first cycle and 219 days for patients with no change. Only five out of 21 patients with no change after one cycle responded to continuous administration of this regimen including one complete remission. In alternating therapy, median survival was 347 days for patients with decrease in tumor size after the first cycle and 378 days for patients with no change indicating no difference in prognosis. Twelve out of 18 patients with no change responded to continuous administration of alternating treatment including six complete remissions. We concluded that response to the first cycle according to chest X-ray is a reliable and prognostically valid response criterion if sequential therapy is used. In this treatment modality no change in tumor size after the first cycle indicates poor prognosis, and improvement of the patients' outcome may be achieved by a switch to a second non-cross resistant drug combination.*

INTRODUCTION

SMALL cell lung cancer (SCLC) shows a high susceptibility to multiple agent chemotherapy resulting in response rates up to 90% [1, 2]. Unfortunately, in the majority of patients response duration is short and relapse is the common outcome. The main reason for poor survival may be the occurrence of drug resistance which may develop during chemotherapy or may even exist before chemotherapy is initiated. Treatment of relapse or primary resistant disease of SCLC is difficult. Chemotherapy protocols generally agree that patients with progressive disease are to be switched to a second-line regimen. In treatment of stable disease it is common practice to administer first-line therapy until progression is noticed [3–7]. Furthermore, first evaluation of response to treatment often is performed after the second or the third cycle, because most physicians believe that evaluation of response at this time is more valid than after each cycle of chemotherapy [8–12].

Thus, particularly in stable disease of SCLC, several cycles of first-line therapy are given prior to the application of second-line regimens.

During the course of a randomized multicenter trial testing alternating treatment in SCLC we observed that most responding patients exhibited a reduction of tumor size after only one cycle of chemotherapy, and some of them achieved a nearly complete remission. Thus, we started an examin-

Accepted 9 April 1987.
The study was supported by the Bundesministerium für Forschung und Technologie.
Participating institutions: Philipps-University Hospitals Marburg; Krankenhaus Rohrbach, Heidelberg; Evangelische und Johanniter-Krankenanstalten, Oberhausen; St.Johannes-Hospital, Duisburg; Klinikum Mannheim; Städtische Kliniken Fulda; St. Elisabethen-Krankenhaus, Ravensburg; Krankenhaus an der Lieth, Bovenden; Justus-Liebig-University Hospitals Gießen; Medizinische Klinik, Kiel; Kreiskrankenhaus Bad Hersfeld; Johann-Wolfgang-Goethe-University Hospitals Frankfurt; Medizinische Hochschule Hannover; Universitätsklinikum Charlottenburg, Berlin.
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ation as to whether evaluation of response could be precise and meaningful in all patients if undertaken 3 weeks after treatment allocation. These results may provide detailed information about the prognostic value of response to the first cycle of chemotherapy and may be helpful to establish some guidelines for treatment of non-responders in order to improve their prognosis.

MATERIALS AND METHODS

In July 1981 a multicenter randomized trial comparing sequential to alternating treatment in SCLC was started. Fourteen German hospitals participated and accrued 306 patients. The study was closed in November 1983.

Eligibility

Eligibility criteria for entry into the study included

(a) histologic proof of SCLC;
(b) signs of measurable or evaluable disease;
(c) performance status of 50% or more according to the Karnofksy scale;
(d) age of 70 years or less; and
(e) informed patient's consent.

Patients were excluded from the study if prior radiotherapy, chemotherapy or surgical treatment had been given, if accessory malignant disease existed or if evidence of renal dysfunction (creatinine > 1.5 mg/dl), chronic hepatic disease (bilirubin > 2.0 mg/dl), advanced respiratory or cardiac insufficiency was found.

Pretreatment investigations

Staging prior to treatment consisted of

(a) a bronchoscopy with biopsy to obtain material for histological examination;
(b) chest X-ray with lung tomography and/or computer tomography;
(c) isotopic bone scan;
(d) unilateral iliac crest bone marrow biopsy;
(e) CT scan of the brain;
(f) abdominal ultrasound and/or a CT of the abdomen; and
(g) blood counts and standard laboratory parameters.

Treatment

Patients were randomized by telephone call to the biostatistics and data center ZMBT, University of Heidelberg, to receive one of the two treatment regimens.

Sequential chemotherapy consisted of eight cycles of CAV (C = cyclophosphamide 1000 mg/m^2 i.v. d 1, A = adriamycin 50 mg/m^2 i.v. d 1, V = vincristine 2 mg i.v. d 1) administered at 3 week intervals.

Alternating chemotherapy consisted of 3 cycles of EVI (cycles 1, 3 and 5) (E = etoposide 80 mg/m^2 i.v. d 1–3, V = vindesine 3 mg/m^2 i.v. d 1, I = iphosphamide 1500 mg/m^2 i.v. d 1–5) alternating with three cycles (cycles 2, 4 and 6) of PAV (P = cisplatinum 90 mg/m^2 i.v. d 1, A = adriamycin 60 mg/m^2 i.v. d 1, V = vincristine 2 mg i.v. d 1) administered in 3 week intervals and followed by the application of CMC (C = cyclophosphamide 1000 mg/m^2 i.v. d 1,22, M = methotrexate 15 mg/m^2 p.o. d 1,4,8,11, C = CCNU 100 mg/m^2 p.o. d 1) in a 6 week cycle.

No maintenance therapy was given to patients achieving complete remission.

Responders received a prophylactic cranial irradition (30 Gy administered in 10 fractions) after three cycles of chemotherapy. After eight cycles of chemotherapy, chest irradiation (45 Gy given in 20 fractions) was applied to patients without distant metastases.

Evaluation of response

Three weeks after each cycle of chemotherapy patients were evaluated with a physical examination, chest X-ray, ultrasound of the abdomen and laboratory parameters. Chest X-ray was coded as "decrease", "no change" or "increase" of primary tumor size, involved lymph nodes and pleural effusion in comparison to the preceeding radiography. No quantitative parameters were measured, because several patients had evaluable but unmeasurable disease. Classification of response was based exclusively on the change of tumor size indicated by chest X-ray. To assess the reliability of the chest X-ray findings a panel of radiologists and oncologists reviewed the roentgenograms obtained before and 3 weeks after start of treatment. Blinding was achieved by covering names and random permutation of the sequence of patients.

Complete restaging was conducted in the same way as pretreatment staging after the third and the eighth cycle of chemotherapy. Bronchoscopy was repeated only if complete remission was suggested.

Management of unresponsive disease during chemotherapy

Non-responders (NC or PROG) receiving sequential therapy were switched to alternating treatment. Non-responders receiving alternating chemotherapy were switched to CAV therapy. Switch to the other treatment regimen was conducted after at least two cycles of chemotherapy. During the study, interim results partly presented here required modification of management of non-responders, i.e. patients rceiving sequential treatment were allowed to cross over to the alternating treatment if unresponsive to the first cycle of CAV application starting in April, 1983.

Table 1. *Patient characteristics*

Characteristics	Sequential therapy		Alternating therapy		Total	
	n	(%)	*n*	(%)	*n*	(%)
Sex						
male	128	(84)	126	(84)	254	(84)
female	24	(16)	24	(16)	48	(16)
Extent of disease						
limited	53	(35)	51	(34)	104	(34)
extensive	99	(65)	99	(66)	198	(66)
Performance status						
Karnofsky 80–100	116	(76)	120	(80)	236	(78)
Karnofsky 50–70	36	(24)	30	(20)	66	(22)
Initial weight loss						
less than 5%	90	(59)	87	(58)	177	(59)
5% of more	62	(41)	63	(42)	125	(41)

Statistical methods

Survival time was chosen as the main criterion and best response as the secondary criterion for the assessment of the prognostic value. The comparison of survival curves was performed by log-rank test, the calculation of P values was based on the two-tailed significance test. Adjustment of prognostic factors in the comparison of survival was achieved by using Cox's proportional hazard model, graphical presentations are based on the Kaplan–Meier method.

RESULTS

Patient population

During a 29 month recruitment period, 306 patients were entered into the study. The minimum time of follow-up was 2 1/2 years. This analysis was based on the data of 302 evaluable patients, 152 receiving sequential and 150 receiving alternating treatment.

Patient characteristics

Individual characteristics of patients and their distribution to the treatment arms are summarized in Table 1. This table shows that treatment groups were well matched for known important prognostic factors.

Response to the first cycle of chemotherapy

Decrease of tumor size after only one cycle of chemotherapy was noticed more often in the alternating arm than in the sequential arm (78% vs. 70%). Stable disease was seen in 25% of the sequentially treated and 19% of the alternatingly treated patients. The number of patients suffering an increase was less than 5% in both treatment groups

Table 2. *Response to the first cycle of chemotherapy*

Response	Sequential therapy		Alternating therapy		Total	
	n	(%)	*n*	(%)	*n*	(%)
Decrease	96	70	109	78	205	74
Stable	34	25	26	19	60	22
Increase	7	5	5	3	12	4
No data	15		10		25	

(Table 2). When the relationship of extent of response to the first cycle and pretreatment patient characteristics was examined patients with stable disease showed similar prognostic factors in both treatment groups. There was a slightly higher proportion of females (15% vs. 9%) and limited stage SCLC (38% vs. 32%) in the stable disease group of alternating treatment compared to the stable disease group of sequential treatment, but this marginal imbalance was insufficient to point to better prognostic factors in the alternating treatment group. For detailed information about the distribution of important prognostic factors see Table 3.

Comparison of best response and response to first cycle

Achievement of partial or complete remission was indicated in the majority of patients by response to the first cycle of chemotherapy. Twenty-nine out of 30 evaluable patients (97%) with CR in sequential treatment and 46 out of 52 evaluable patients (88%) with CR in alternating treatment were identified by a decrease in tumor size after the first cycle. In patients with PR a decrease was noticed in 87% in sequential and 79% in alternating treatment (Table 4).

If no reduction in tumor size was seen, complete remission later on in treatment was seen in only one

Table 3. Patient characteristics according to response to the first cycle

	Sequential therapy			Alternating therapy		
	Response to the first cycle					
	Decrease $n = 96$ (%)	Stable $n = 34$ (%)	Increase $n = 7$ (%)	Decrease $n = 109$ (%)	Stable $n = 26$ (%)	Increase $n = 5$ (%)
Sex						
female	22	9	0	17	15	0
male	78	91	100	83	85	100
Extent of disease						
limited	40	32	71	34	38	40
extensive	60	68	29	66	62	60
Performance status (Karnofsky)						
80–100	77	82	100	82	85	40
50–70	23	18	0	18	15	60
Initial weight loss						
less than 5%	62	62	57	58	62	60
5% or more	38	38	43	42	38	40

Table 4. Comparison of best response and response to the first cycle

	Sequential therapy response to 1st cycle				Alternating therapy response to 1st cycle			
Best response	Decrease	Stable	Increase	n.d.	Decrease	Stable	Increase	n.d.
CR	29	1	0	2	46	6	0	1
PR	45	7	0	5	38	7	3	3
NC/PROG	22	26	7	8	25	13	2	6

n.d. = no data.

out of 41 sequentially treated patients, but in six out of 31 alternatingly treated patients. An additional six patients in sequential and an additional 10 patients in alternating treatment achieved partial remission later on in the treatment.

Comparison of survival and response to first cycle

In the sequential treatment group decrease in tumor size after the first cycle had a striking impact on survival. Median survival for patients with no change of tumor size (219 days) was distinctly shorter than median survival for patients with decrease (323 days). The comparison of survival curves by means of Cox's proportional hazard model gave a statistically significant difference ($P < 0.01$). In the alternating treatment group median survival of patients with stable disease after the first cycle (378 days) did not differ from median survival of patients with decrease (347 days). Only patients with increase had a poor median survival (252 days). These results are summarized in Table 5. The corresponding survival curves are shown in Figs 1 and 2. When the survival curves of patients with decrease and no change after the first cycle were analyzed separately for limited and extensive disease, the aforementioned results were the same in both subgroups, i.e. response to the first cycle was of crucial prognostic value in sequentially treated patients in limited and extensive disease, whereas tumor reduction was of less importance in alternating treatment for both subgroups. For interpretation of these results it has to be taken into account that the total number of patients with limited disease and no change in tumor size after one cycle was small in sequential (11 patients) as well as in alternating therapy (10 patients). A separate analysis by performance status stratification was not performed because of the small number of patients with low Karnofsky score and no change after the first cycle (see Table 3).

Response to continuous application of first-line therapy in non-responders to the first cycle

In sequential treatment 21 out of 41 non-responders to the first cycle received continuous CAV therapy and were not switched to second-line treatment within the period of induction therapy. Response was rare in these cases. One patient achieved CR and an additional four patients PR. Median survival of these 21 patients was 203 days. In alternating treatment 18 out of 31 non-responders to the first cycle were not switched

Table 5. Comparison of survival and response to the first cycle

Survival	Response to the first cycle							
	Sequential therapy				Alternating therapy			
	Decrease	Stable	Increase	Total	Decrease	Stable	Increase	Total
Median survival (days)	323	219	181	298	347	378	252	344

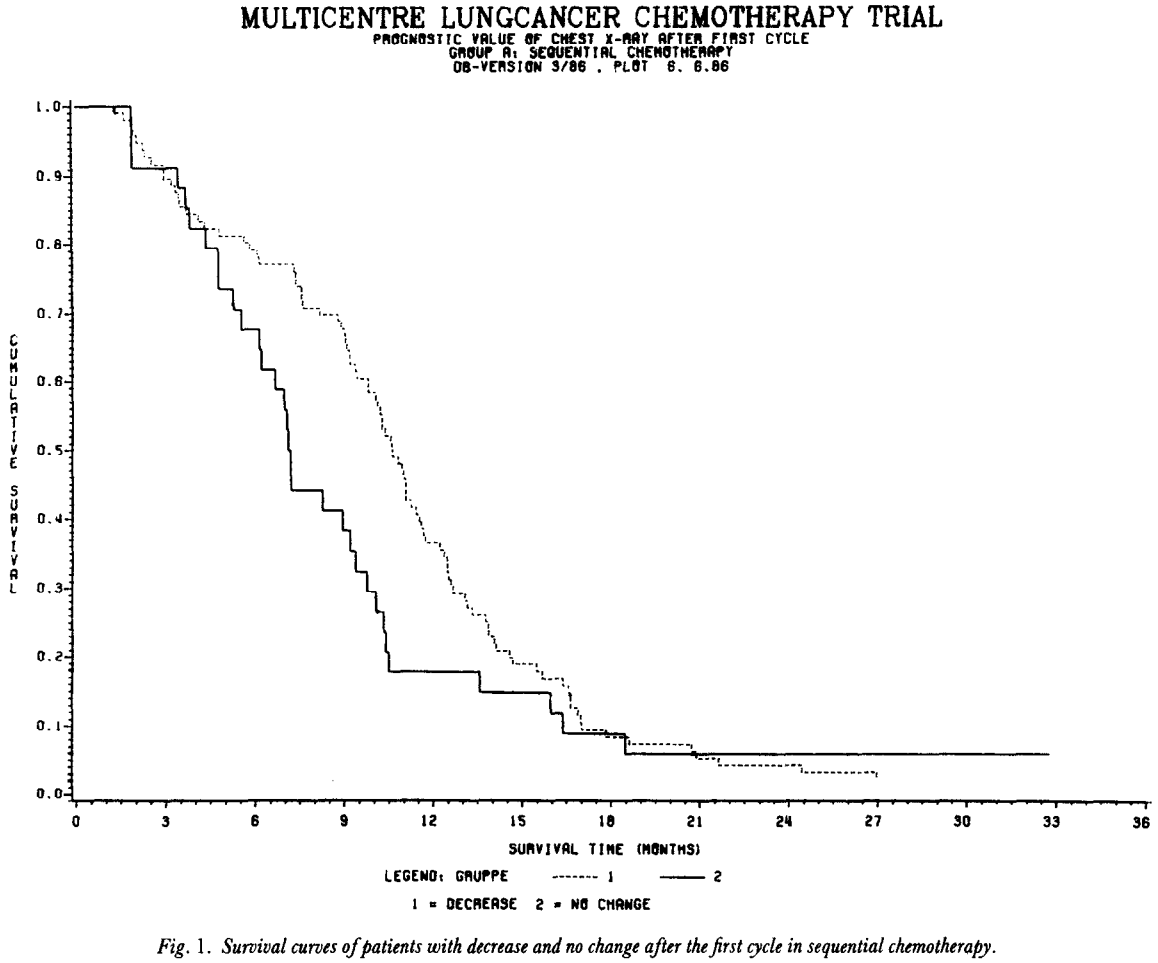

Fig. 1. Survival curves of patients with decrease and no change after the first cycle in sequential chemotherapy.

to the other regimen during induction therapy. Complete remission was seen in six of them, and an additional six patients achieved PR. Median survival of these 18 patients was 292 days. Thus, benefit of continuous CAV therapy in non-responders to the first cycle was small, whereas 66% of the non-responders to the alternating regimen profited from its continuous application (Table 6).

Response to second-line therapy

Non-responders to first-line therapy were switched to second-line chemotherapy. Most of them were not switched to second-line therapy immediately after the first cycle, but received first-line therapy until progressive disease occurred or stable disease was seen during several cycles. Management of treatment was the same in patients who responded to the first cycle but suffered progressive or stable disease later on in treatment. All these patients were taken together when response to second-line therapy was evaluated. Thus, during induction therapy, a total of 47 non-responders to sequential treatment and 21 non-responders to alternating treatment were switched to the other regimen.

Table 7 gives the number of cycles of first-line chemotherapy given before crossing over to the other regimen. This table indicates that 75% of the non-responders in sequential treatment and 100% of the non-responders to alternating treatment received at least three cycles of first-line therapy before crossing over. Twenty-nine of the 47 non-responders to CAV benefited by shifting to alternating treatment, whereas only eight out of 21 non-

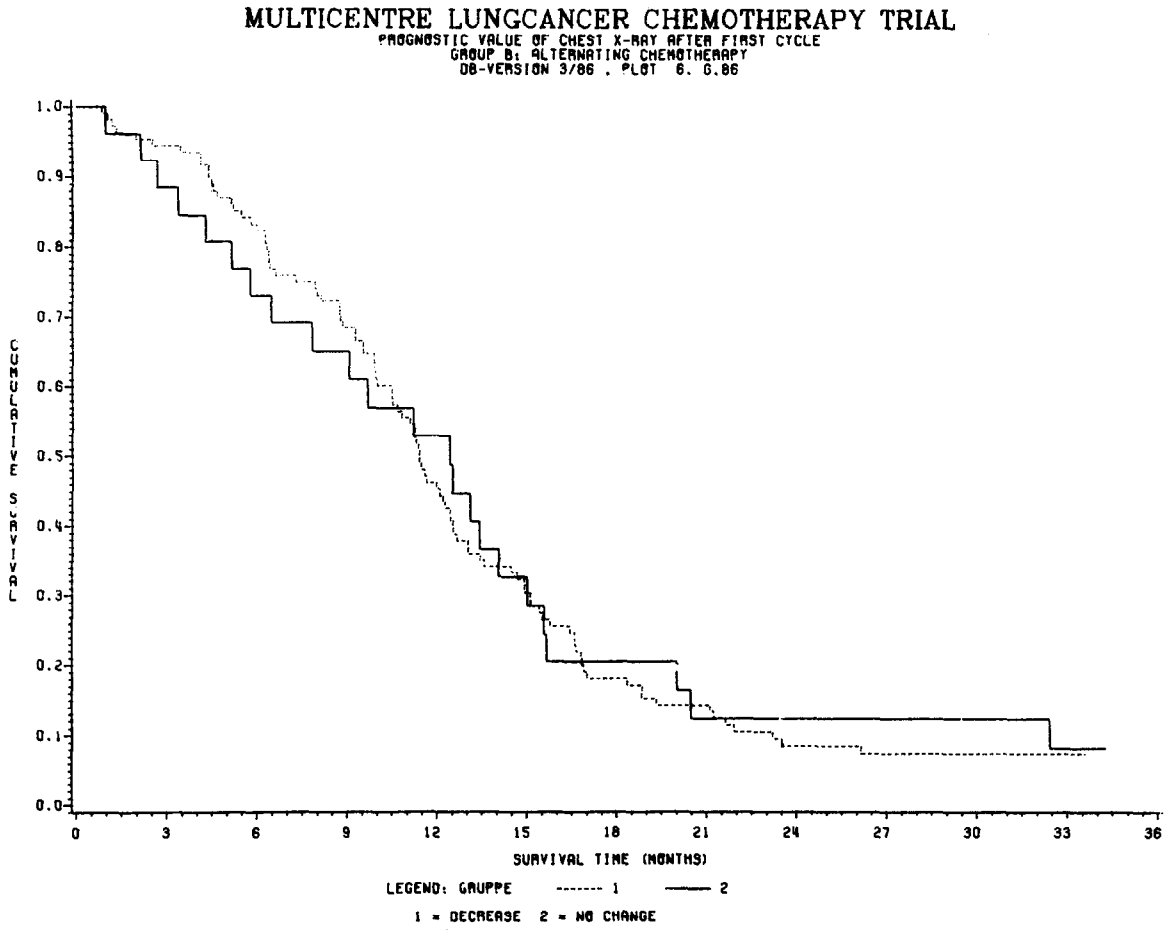

Fig. 2. Survival curves of patients with decrease and no change after the first cycle in alternating chemotherapy.

Table 6. Response to continuous application of front-line therapy

	Sequential therapy $n = 21$		Alternating therapy $n = 18$	
	n	%	*n*	%
CR	1	5	6	33
PR	4	19	6	33
NC/PROG	16	76	6	33
Median survival	203 days		292 days	

Table 7. Number of cycles given before crossing over to second-line therapy

No. of cycles	Sequential therapy *n*	%	Alternating therapy *n*	%
1	3	6	—	—
2	9	19	—	—
3	11	23	5	24
4	6	13	7	33
5	9	19	3	14
6	4	8	3	14
7	2	4	—	—
No data	3	6	3	14

Table 8. Response to second-line therapy in progressive and stable disease

	First line therapy			
	Sequential therapy $n = 44$		Alternating therapy $n = 20$	
Response	*n*	%	*n*	%
Complete remission	—	—	—	—
Partial remission	13	20	2	10
Minor response	16	36	6	30
No response	15	34	12	60

responders to alternating treatment profited by crossing over to CAV. There was no complete remission seen after crossing over in both treatment groups, but the rate of partial remissions was 30% for patients shifting from CAV to alternating treatment vs. 10% for patients shifting the other way (Table 8).

If patients with stable or progressive disease receiving CAV were switched to the alternating regimen they reached a median survival of 295 days. Responders to second-line therapy showed a longer median survival (307 days) than non-responders (241 days). However, these survival times were superior to the survival of patients with

stable disease after one cycle receiving continuous CAV therapy.

If patients with stable or progressive disease receiving alternating treatment as front line therapy were switched to CAV, median survival was 295 days with a longer median survival for responders (307 days) than for non-responders (217 days). This median survival was not superior to the survival of patients with no change after the first cycle receiving continuous alternating therapy (378 days).

DISCUSSION

Small cell lung cancer is known as a tumor entity which exhibits rapid tumor growth and dissemination. Because of these characteristics we suggested that active drug combinations may be able to change tumor size within a short period to time. To confirm this hypothesis we examined whether evaluation of response after one cycle of chemotherapy is a precise and meaningful response criterion in SCLC. Our results show that no response to the first cycle was connected with poor survival in sequentially treated patients, but not in patients with alternating treatment. In the latter group prognosis of patients with decrease or stable disease after the first cycle did not differ.

Longer survival times for patients with response to chemotherapy compared with patients without response are well known and rather standard observations. Recently, in a consensus report of the International Association for the Study of Lung Cancer [13], it was suggested that the demonstration of differences in survival between responders and non-responders should no longer be considered necessary. Furthermore, Weiss *et al.* [14] have described methodological and interpretational difficulties connected with the analysis of the relationship between response and survival. In our opinion, one important point of criticism is the lack of clinical consequences which are drawn from these results. An analysis of survival in responders and non-responders would only be helpful if new therapeutic guidelines could be established by this approach. Improvement of therapy based on response-related comparisons would require (a) a prognostically valid response criterion, which is defined objectively and which is evaluated at fixed points of time early in treatment course, and (b) effective treatment strategies for non-responders.

The data presented here demonstrated that decrease in tumor size in chest X-ray after only one treatment cycle is a reliable and prognostically valid measure of response. Being aware of the difficulties in interpretation and reproductibility of assessment of chest X-rays, the roentgenograms taken before and 3 weeks after treatment allocation were reviewed by a panel of radiologists and oncologists. When response to chemotherapy was classified as decrease, stable or increase, there was only one disagreement between the judgement of the local radiologist and the review panel. If chest X-rays were taken exactly at the beginning of treatment, evaluation of response was easier than if taken several days prior to treatment allocation. Within a week or more tumor growth may have increased tumor size. In these cases chest X-rays may not be able to demonstrate a reduction of tumor size after the first cycle of chemotherapy although the tumor responded to the therapy. Thus, for evaluation of response it is absolutely necessary to take a chest X-ray exactly at the beginning of treatment.

The evaluation of response by chest X-ray was independent of whether the tumor was measurable or evaluable before treatment. This corresponds to the results of Eagan *et al.* [15] which show that in patients with advanced non-small cell lung cancer measurable tumor regressions were comparable to evaluable regressions with respect to their incidence as well as their prognostic value. Thus, assessment of response by chest X-ray only 3 weeks after treatment allocation was practicable and reproducible.

A decrease in tumor size after the first cycle was seen in the majority of patients achieving complete or partial remission at any time during treatment. In sequential treatment response to the first cycle strongly influenced best response and survival. Only one out of 32 patients with complete remission and seven out of 57 patients with partial remission had stable disease after the first cycle. Median survival was significantly longer in patients with decrease than in patients with no change or increase. This may be mainly caused by the existence of drug resistance in patients with no change. SCLC is a rapidly growing tumor which is highly sensitive to chemotherapy. It is well known that aggressive chemotherapy reduces tumor burden in rapidly growing tumors within a short period of time. Active drug combinations may reduce tumor size also in SCLC within 3 weeks after the onset of treatment. The presence of no change or increase after the first cycle may indicate no or less sensibility of the tumor to the regimen applied, i.e. drug resistance at least in part.

In alternating treatment response to the first cycle was of less importance for best response and survival. Six out of 53 patients with complete remission and 10 out of 51 patients with partial remission had no reduction in tumor size after one cycle. Survival curves of patients with decrease and stable disease after the first cycle were nearly identical, and similar to the survival of patients with decrease in the sequential treatment arm. Thus, patients with stable disease after the first cycle had favorable survival in alternating treatment, but unfavorable survival in sequential treatment. The

heterogeneity of patient characteristics was unlikely to be the reason for this difference since known important prognostic factors were well balanced between non-responders in both groups. Additionally, the influence of second-line therapy after crossing over was small. Only 12 out of 34 patients with no change after the first cycle in sequential treatment and four out of 26 patients with no change in alternating treatment were switched to second-line therapy. A switch to the other regimen was performed predominantly after at least three cycles of first-line therapy had been administered. Therefore, we conclude that the better prognosis of patients with no change in the alternating treatment group may be caused by the regular administration of an additional two different drug combinations. This suggestion was confirmed by the analysis of response to the continuous application of the randomized therapy in non-responders to the first cycle. Delayed response to CAV was rare and median survival was 203 days for these patients. On the other hand, delayed response to alternating treatment was seen more frequently, and median survival was 292 days. If the first drug combination in alternating treatment (EVI) failed to work, response to the second cycle (PAV) was seen in 40%. Thus, the application of two different "not cross-resistant" drug combinations seems to be the main reason for the favorable survival of patient with no change after the first cycle in alternating treatment.

Another point has to be considered additionally. The design of the study compared sequential CAV therapy to an alternating regimen consisting of three drug combinations different from CAV. The alternating regimen was superior to CAV with respect to response to the first cycle (78% vs. 70%), complete remission rate (36% vs. 21%) and survival. Median survival was 11.3 months vs. 9.8 months for all patients, 13.4 months vs. 11.1 months for limited disease and 9.9 months vs. 8.9 months for extensive disease, all in favor of alternating treatment. Because different drug combinations with different response rates were given during the first cycle, the more active drug combination EVI may have delayed tumor growth more than the less active CAV regimen although stable disease was seen after the first cycle in both groups.

To find out whether survival differs between both treatment groups although objective response was the same, we analyzed survival in relationship to best response. Survival only depended on the extent of response irrespective of the regimen applied. Therefore the superiority of the alternating schedule may be due to the higher response rate, in particular the higher complete remission rate in this group.

Thus, the favorable prognosis of patients with stable disease after one cycle of alternating treatment was most likely caused by the high response rates these patients achieved later on in treatment, whereas response to continuous CAV therapy was rare in patients with stable disease after one cycle and therefore resulted in poor survival.

Possible clinical implications of this analysis are derived from the response to the second-line therapy. In particular, patients receiving CAV treatment as front-line therapy seemed to benefit from crossing over to alternating treatment. Partial remission was seen in 30% of these patients and the median survival for all patients crossing over during induction therapy was 295 days which is clearly superior to the median survial of non-responders to the first cycle receiving continuous CAV therapy (203 days).

The results of this analysis indicate that the assessment of response after only one cycle of chemotherapy is practicable and has crucial prognostic value if a sequential treatment mode is administered. Decrease in tumor size indicates the activity of the drug combination applied and these patients have a good chance of achieving partial or complete remission by administration of this regimen. In patients with no change in tumor size, attainment of partial or complete remission is rarely achieved by continuous application of the same regimen. These patients should be switched immediately to a second-line therapy in order to offer them a second chance. In future clinical trials we will test this strategy for treatment of SCLC.

Acknowledgements—The authors wish to thank Mrs. C. Braun for assisting in data collection and careful preparation of this manuscript. The excellent collaboration of the Biostatistics and Data Center (ZMBT), University of Heidelberg, in collection and analyses of the data presented is also acknowledged.

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