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Chemotherapy of Small Cell Carcinoma of the Lung: Comparison of a Cyclic Alternative Combination with Simultaneous Combinations of Four and Seven Agents

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Abstract—*It would appear to be of advantage to treat patients with anaplastic small cell carcinoma with an alternating sequence of non cross-resistant agents. This was explored in two randomized clinical trials involving 142 previously-untreated patients. In the first trial a simultaneous 4-drug combination (regime A) was compared with an alternating sequence of a combination of 4 phase non-specific agents and a combination of 3 phase specific agents (regimen B). In the second trial regimen B was compared with a simultaneous combination of the same 7 agents. In regimen A methotrexate (MTX), vincristine (VRC), cyclophosphamide (CPA) and procarbazine (PCZ) were given for 6 weeks, then for 2 weeks every 4 weeks. In regimen B adriamycin, CCNU, CPA and PCZ were followed after 3 weeks by MTX, VCR and hydroxyurea. The sequence was recycled at 8-week intervals. In regimen C the 7 drugs were given in the first week and repeated every 4 weeks. After 24 weeks of induction, patients with response or stabilization either received or did not receive a maintenance treatment with 3 or 4 of the induction drugs. The tumor response was evaluated after the initial 8 weeks of treatment. The response rates for A, B and C were not significantly different and ranged between 60 and 73%. Performance status and tumor extension did not influence the response rate. The survival was significantly related to the tumor response, the performance status and the tumor extension. The overall median survival was slightly more than 6 months. The longest median survival (43 weeks) was found in patients with responsive locoregional tumors. The analysis of survival as per treatment regimen, performance status and tumor extension showed no advantage for the alternative treatment. Toxicity was moderate and equivalent in A, B and C. It is concluded that the response rate and survival achieved with an alternating combination chemotherapy of moderate toxicity in small cell lung cancer are not superior to those observed with simultaneous combinations of equivalent intensity.*

INTRODUCTION

RESPONSE rates greater than 60% are frequently observed in multiple drug chemotherapy of small cell carcinoma of the lung[1, 2]. However, the effects of this treatment on survival remain generally disappointing. Early treatment failures following an apparently complete disappearance of the tumor are frequent and suggest that the therapeutic significance of a complete response is not identical for small cell carcinoma of the lung and for many other tumor types. Recently, a greater proportion of long survivors and an increased rate of complete responders was obtained with more intensive drug dosages at the cost of a more severe toxicity. This better effect on response and survival is probably due to a higher initial cell kill effect, at a time when drug resistance is not yet able to play a negative part. Another way to improve the therapeutic

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effectiveness would be to alternate non cross-resistant drug regimens, thus delaying the appearance of resistance, and possibly also inducing, through the alternation, a cycle active mechanism such as the one previously described by Schabel[3] and already investigated by others[4, 5].

The object of the present study was to evaluate the therapeutic effectiveness of a low dose alternating sequence of non cross-resistant drug combinations in small cell carcinoma of the lung by randomized comparison with simultaneous drug combinations of equivalent toxicity. A low level of drug toxicity was selected for two reasons: to allow for treatment on an out-patient basis, and to explore specifically whether the alternation of non cross-resistant treatments could improve the effectiveness without increasing the level of drug toxicity.

MATERIALS AND METHODS

All patients with cytologically or histologically proven anaplastic small cell carcinoma seen at the member institutions of the Swiss Group (SAKK) were eligible. Further criteria for admission were tumor lesions, measurable in two perpendicular diameters or evaluable in only one diameter, a performance status (ECOG rating) of 0–3, serum creatinin below 13 mg/liter, serum bilirubin below 20 mg/liter and leucocyte and thrombocyte counts of at least 3500 and 150,000 per mm^3 respectively. Tumor measurements, toxicity, blood counts, and renal and liver function tests (bilirubin, transaminases, alkalin phosphatase) were registered at onset and every 2 weeks during treatment. Radiographic controls were repeated every 1–2 months for thoracic lesions and every 2–4 months for skeletal lesions. A radiologic bone survey or bone scan was required before treatment. Bone marrow and liver biopsies were optional. Anamnestic data, patient and tumor characteristics, tumor localizations and measurements, serial observations and final evaluation of treatment were recorded on standardized forms. The treatment was determined for each patient by randomization after stratification for institution and performance status (0–1 or 2–3), according to randomization log lists.

The criteria used for evaluation of treatment results were objective response and survival from the first day of treatment. The following response categories were defined: complete response: the complete disappearance of all measurable and/or evaluable tumor parameters without appearance of new lesions; partial response: a reduction by 50% or more of the sum of the diameters of all measurable parameters and a corresponding reduction of all evaluable parameters without appearance of new lesions; no change: no modification of measurements, or minor changes without appearance of new lesions; progression: an increase by 50% or more of the sum of diameters or of the diameter of measurable or evaluable parameters, or the appearance of new tumor lesions.

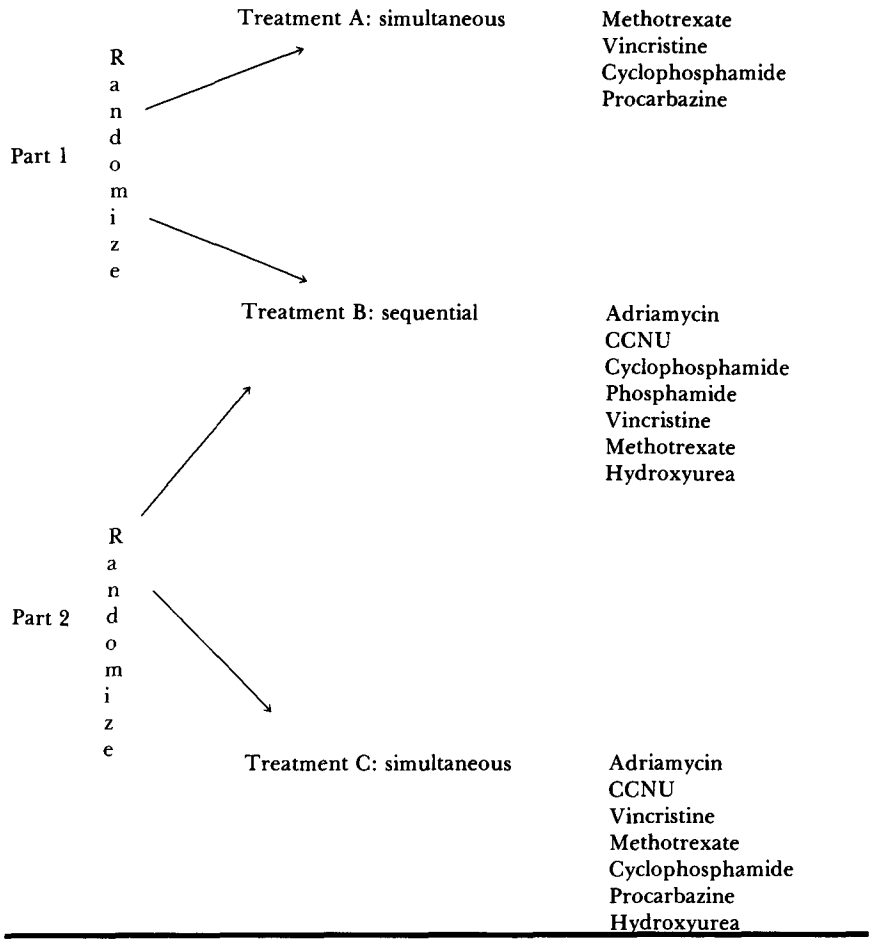
Patients with the following conditions were considered as not evaluable: treatment duration of two weeks or less, inevaluable tumor lesions, treatment refusal and major protocol violations. The assessment of objective response was made by comparing tumor criteria present on day one and at the end of the eighth week of treatment. Transient tumor changes occurring before that end point were not considered. For the statistical analysis of survival a log rank test, as described by Peto *et al.*[6], was used for the comparison of Kaplan–Meyer actuarial survival curves.

Treatment

The study was conducted in two parts (Table 1). In the first part, the patients were randomized to receive either treatment A or treatment B as follows: treatment A: methotrexate, 25 mg/m^2 i.v., weekly for 6 weeks; vincristine, 1.3 mg/m^2 i.v., weekly for 4 weeks; cyclophosphamide, 70 mg/m^2 orally, daily and procarbazine, 70 mg/m^2 orally, daily for 6 weeks. The treatment was followed by a 2-week rest period and resumed at the same doses for 2 weeks every 4 weeks, with a total duration of 24 weeks. Treatment B: adriamycin, 30 mg/m^2, i.v., day 1; CCNU, 70 mg/m^2 orally, day 1; cyclophosphamide, 70 mg/m^2 orally, days 1–7. After a 3 week rest period it was followed by vincristine, 1.3 mg/m^2 i.v., days 1 and 8; methotrexate, 25 mg/m^2 i.v., days 1 and 8; and hydroxyurea, 1000 mg/m^2 orally, days 1, 3, 5, 8, 11 and 13. The whole cycle was repeated three times at 8 week intervals. At the end of this 24-week treatment period all patients with complete response, partial response or stable disease were randomized to receive either no further treatment or treatment with regimen A for 2 weeks every 4 weeks until relapse or death.

In the second part of the study, the patients were randomized to receive either treatment with regimen B or a simultaneous combination of the same 7 drugs (treatment C) as follows: adriamycin, 25 mg/m^2 i.v., day 1; CCNU, 60 mg/m^2 orally, day 1; vincristine 1.3 mg/m^2

Table 1



i.v., day 1; methotrexate, 25 mg/m^2 i.v., day 1; cyclophosphamide, 70 mg/m^2 orally, days 1–7; procarbazine, 70 mg/m^2 orally, days 1–7; hydroxyurea, 1000 mg/m^2 orally, days 1, 3, 5. This treatment was repeated every 4 weeks for 24 weeks. All patients with complete response, partial response or stable disease at the end of the 24 week period received the following maintenance treatment: methotrexate, 35 mg/m^2 i.v., day 1; vincristine, 1.3 mg/m^2 i.v., day 1; and cyclophosphamide, 700 mg/m^2 i.v., day 1 every month until relapse or death.

All data were centrally registered at the Group Operation Office at 6 month intervals. All patients were followed until death and their date of death (year, month and day) registered. The reasons for any follow-up losses were reported. No attempt was made to register subsequent anti-tumor treatments in detail.

RESULTS

One hundred and forty-two patients were entered into the study. Seventy-two were included in the first part of the trial and 70 patients in the second part. Seventeen were considered not evaluable: 10 for treatment duration of 2 weeks or less and 7 for one of the other reasons stipulated in the protocol. The composition of the patient population and the distribution of the major prognostic factors are given in Table 2. There are no significant differences in the treatment groups with regard to sex, age, time interval from diagnosis to onset of protocol treatment or previous treatment. Patients with disease limited to the lung and regional lymph nodes are in excess in treatment group C. This difference is significant for $P = 0.05$. Also, group A has relatively few patients with a good performance status. This last difference is not significant. Sites of metastases are equally distributed, with the exception of the central nervous system. Because of the uneven distribution of prognostic factors influencing patient survival the comparison of treatment groups was made separately for limited and extensive disease and according to the performance status category.

Table 2. Characteristics of evaluable patients by treatment groups

		A	B	C
Sex (male/female)		29/1	59/6	27
Median age (years)		58.5	59.5	62.0
Median time from diagnosis (months)		1	1	1
No. with previous surgery		0	0	2
No. with previous radiation therapy		6	8	1
No. with previous chemotherapy		1	4	1
Mean performance score		1.7	1.4	1.2
No. with loco-regional tumor		10	23	19
No. with extensive tumor		20	42	11
Involved organs:	liver	10	18	5
	bones	5	11	2
	CNS	3	8	2
	pleura	4	4	5
	skin	3	5	2
No. of patients		30	65	30

Tumor response

The responses of the treatment groups are shown in Table 3. The overall response rates range between 60 and 73%. The observed differences do not reach the level of statistical significance. For complete responses the rates vary from 17 to 33% and there is a difference at the 0.10 level (χ^2 test) between treatment A and treatment B. As shown in Table 4, performance status and extension of disease do not influence the rates of response or complete response significantly. Twenty-four of the 45 non-responders had progressive disease during the first 8 weeks of treatment.

Table 3. Responses by treatment groups

	A	B	C
No. of evaluable patients	30	65	30
No. of complete responses	10	11	7
No. of partial responses	12	29	11
No. of no change	3	10	8
No. of progression	5	15	4
% responses	73	62	60
% complete responses	33	17	23

Table 4. Responses by performance status and tumour extension

	Complete response (%)	Complete + partial response (%)
Performance status 0–1	21.3	67.2
Performance status 2–3	23.4	60.9
Locoregional tumor	21.2	59.6
Extensive tumor	23.3	67.1

Maintenance treatment

In the first part of the study, 15 patients were still in remission or stabilization at the end of the first 24-week period. Seven were allocated to the control group and 8 received maintenance treatment for 3–108 weeks. The time of relapse varied from 26 to more than 250 weeks for the maintenance treatment group and from 25 to more than 215 weeks in the control group. The survival from onset of the induction treatment varied from 35 to more than 250 weeks in the maintenance treatment group and from 30 to more than 215 weeks in the control group. The small number of patients does not allow for statistical analysis. There is no obvious difference between the maintenance and the control group with respect the the duration of remission or survival.

In the second part of the study, 12 patients entered the maintenance phase. Eleven received the maintenance treatment for a duration varying from 1 to more than 114 weeks. Survival was from 32 to more than 174 weeks.

Survival

Table 5 indicates that the median survival time is significantly related to the therapeutic response, the performance status score and the extension of the tumor. The overall median survival time is slightly more than 6 months. The best figure is observed in patients with complete response of a tumor of locoregional extension (43 weeks), and the poorest in non-responders with extensive tumor (14 weeks). Figure 1 shows that the survival curves of the sequential treatment groups in the first and second parts of the study are identical. On this basis all evaluable patients in treatment group B are considered as one group in the comparison of survival, in spite of the fact that the maintenance treatment was not the same in all patients. The survival curves in the 3 treatment groups are shown in Fig. 2. The median survival time is 31.4 weeks in group A, 23.7 weeks in group B and 34.0 weeks in group C. The difference is significant between group B and

Table 5. Median survival time (weeks) by treatment response performance status and tumor extension

	CR	PR	O+P	All Pts
All patients	38.8‡	29.3‡	16.0‡	28.7
Performance status 0–1	35.5	29.3	27.6†	30.5*
Performance status 2–3	40.5	29.3	14.0†	24.3*
Locoregional tumor	43.1§	32.0	23.0‖	31.3
Extensive tumor	32.5§	28.3	31.0‖	25.6

*, †, ‡, §, ‖: Significant difference ($P < 0.05$).

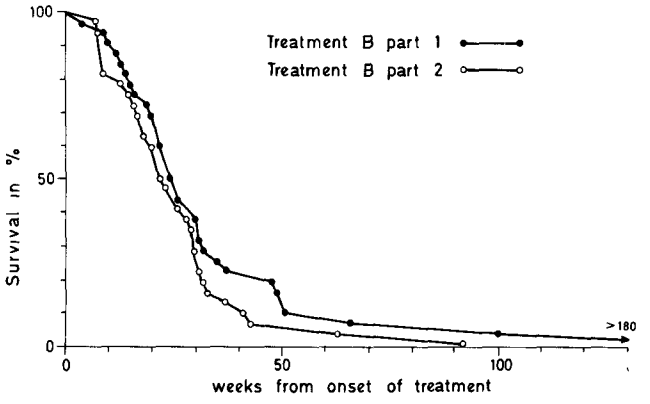


Fig. 1. Comparison of actuarial survival curves of the patient groups treated with the alternating regimen in the first and second parts of the trial.

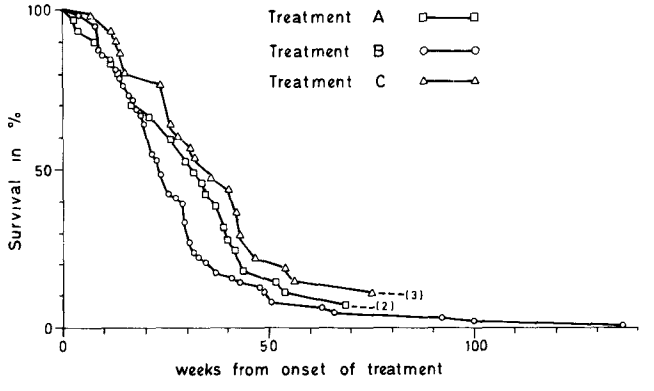


Fig. 2. Comparison of actuarial survival curves of the patient groups treated with a simultaneous 4-drug combination (treatment A), an alternating regimen (treatment B) and a simultaneous combination of 7 drugs (treatment C). Numbers between brackets correspond to the number of patients still alive at the end of the observation period.

group C ($P < 0.05$). Subcategories with good or poor performance status and with locoregional or extensive tumors were analyzed separately. There are significant differences for patients with good performance status and patients with extensive disease. In both cases the survival is shorter in the sequential treatment group B (Table 6). Survivors of 18 months or more are shown in Table 7. They represent 7% of all patients. Two were initially complete responders and 7 were partial responders. There is no evidence of a predominance for a treatment regimen, performance status or initial disease extension.

Table 6. Median survival time (weeks) by treatment, performance status and tumor extension

Patients	A	B	C	*P* value
All	31.4	23.7	34.0	0.027
Performance status 0–1	34.0	29.2	38.7	0.031
Performance status 2–3	20.3	21.0	29.5	0.595
Locoregional tumor	26.0	27.5	34.5	0.795
Extensive tumor	32.4	21.5	30.0	0.025

Table 7. Characteristics of patients still alive after 18 months or longer

	No. of patients
Treatment (A/B/C)	3/8/3
Initial tumor response (CR/PR)	2/7
Maintenance treatment (yes/no)	4/5
Performance status (0–1/2–3)	4/5
Locoregional/extensive tumor	5/4

Toxicity

Drug-induced toxicity is summarized in Table 8. Myelosuppression was the main dose-limiting toxicity in all treatment groups. No major differences were observed in the nadir

Table 8. Toxicity scores

	Mean toxicity score*			
	1/A	1/B	2/B	2/C
Hematologic	1.97	1.59	1.79	1.76
Digestive	1.70	1.41	1.30	1.64
Neurologic	0.60	0.59	0.09	0.22
Alopecia	0.90†	0.84	1.36	1.36

*Leucocytes/mm³: 4000 = 0
3000–3999 = 1
2000–2999 = 2
1000–1999 = 3
0– 999 = 4
Thrombocytes/mm³: 140000 = 1
110000–139999 = 1
70000–109999 = 2
30000–69999 = 3
0–29999 = 4.

Other toxicities: 0 = no toxicity; 1 = mild; 2 = moderate; 3 = severe; 4 = life threatening.
†1 toxic death.

counts for WBC and platelets. The nadir blood counts registered during the first 8 weeks were lower than those observed later on. This can be explained by the dose reductions after the first occurrence of hematologic toxicity. Gastrointenstinal toxicity consisted mainly of nausea and vomiting, with occasional mucositis. It was most pronounced with regimen A. Nausea and vomiting occurred either as an acute side effect within a few hours after intravenous chemotherapy or was long-lasting and progressive, leading to dose reduction or even discontinuation of the entire anti-tumor treatment. Neurologic toxicity corresponded to what is generally observed with vincristine, with peripheral neuropathy, asthenia, jaw pains and obstipation. Alopecia was frequent but never caused modification of the treatment. One patient died after 20 weeks of treatment with generalized bleeding secondary to drug-induced thrombocytopenia. In all other patients drug toxicity was reversible. No long-lasting marrow depression or low blood counts were observed after cessation of therapy.

DISCUSSION

In this study a sequentially alternated combination including seven chemotherapeutic agents is compared in terms of patient survival and tumor response with either a simultaneous combination of four, or a simultaneous combination of all seven agents. With a total number of 125 evaluable patients, the therapeutic results in the three treatment groups are not significantly different and there is, in particular, no advantage for the alternated regimen. The length of patient survival is significantly related to the performance status and the disease extension, as defined at the onset of the study of the treatment, and also the tumor response. Unfortunately, in this series tumor extension and performance status are not equally distributed within the compared groups. For this reason, patients with the same performance status or the same disease extension have been analyzed separately. In none of these subgroups is response or survival any better for patients with the alternated treatment. The 9 patients with a survival of more than 18 months are equally distributed in the three treatment groups. There are no significant differences in the rates of response or complete response in the three treatment groups. The response rate is not related, in this series, to the performance status or the tumor extension.

The alternated treatment schedule used here was defined according to a theoretical model previously proposed by Schabel[3]. In this model, a phase non-specific treatment and a phase specific treatment are alternatively repeated. Each time the total tumor cell population is reduced by the phase non-specific treatment, the growth fraction in the residual tumor is supposed to increase so that the next application of the phase specific treatment would be more efficient. From the seven agents used here, cyclophosphamide, procarbazine, lomustine and adriamycin were considered as phase non-specific agents, whereas vincristine, methotrexate and hydroxyurea were classified as phase specific agents[7]. This classification is based on the rather crude theoretical assumption that alkylators, nitrosoureas and intercalating agents have cell-phase non-specific mechanisms of action and that inhibitors of the synthesis of nucleic acids or microtubules have a cell phase specific cytotoxicity. Such an oversimplification of the relationships between cytotoxicity and cell proliferation is liable to criticism[8]. Thus, the lack of advantage for the alternated regimen in this study has no bearing with the validity of Schabel's model, but only demonstrates that the translation of a theoretical model into a clinical application may be disappointing.

The drug toxicity was mild to moderate, and equivalent in the 3 treatment groups. Thus, the absence of advantage for the alternating regimen in terms of treatment response or survival cannot be explained by differences in the intensity of the compared regimens.

The results obtained here with the four-drug combination are quite similar to those previously published by the Swiss Group with the

same regimen[9]. It is concluded from the present data that the alternative use of different drug combinations, or an increase in the number of simultaneously combined agents could not significantly improve the response rate or the survival previously obtained with a low-dose four-drug combination in the treatment of patients with small cell carcinoma of the lung.

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