Continuous versus Alternating Combination Chemotherapy for Advanced Small Cell Carcinoma of the Lung

Kell Østerlind, Sverre Sörenson, Heine H. Hansen, Per Dombernowsky, Fred R. Hirsch, Mogens Hansen, and Mikael Rørth

The Finsen Institute, Copenhagen, Denmark [K. Ø., H. H. H., F. R. H., M. H. M. R.]; Renstromska Hospital, Gothenburg, Sweden [S. S.]; and Medical Department C, Bispebjerg Hospital, Copenhagen, Denmark [P. D.]

ABSTRACT

In a 2-year period, 146 patients with small cell carcinoma of the lung, staged as having extensive disease, were randomized to receive either continuous chemotherapy consisting of (a) 1- (2-chloroethyl)-3-cyclohexyl-1-nitrosourea, cyclophosphamide, methotrexate, and vincristine followed by (b) 4’-demethylepipodophyllotoxin 9-[4,6-C-(R)-ethylidene-β-D-glucopyranoside] and doxorubicin at progression of disease or a regimen of (a) alternating with (b). Seventy-six patients received the continuous regimen; 70 patients received alternating treatment. Response rates were 68 and 72%, respectively. The median duration of response was 16 weeks in patients receiving continuous treatment compared to 28 weeks in patients receiving alternating treatment (p < 0.05). No survival time difference was observed between the groups, median survival being 36 and 38 weeks, respectively. Four patients became long-term survivors (5.6+, 5.5+, 5.1, and 4.7+ years). All received alternating therapy. Six toxic deaths were observed among patients receiving continuous therapy compared to only one death among those in the alternating regimen. In conclusion, alternating combination chemotherapy leads to prolonged duration of remission. Duration of survival is not prolonged in uncured patients, but an increased possibility of long-term disease-free survival cannot be precluded.

INTRODUCTION

Cure is still a rare end point in chemotherapy of lung carcinomas, although sensitive tumors are found among all histological types. SCC constitutes a distinct entity in which it is possible to obtain, through chemotherapy, clinical disease-free status in 20 to 40% of patients and a greater than 50% reduction of tumor in a further 40 to 60% of patients (12). Correspondingly, the median survival is prolonged by a factor of 4 to 5, and the rate of long-term disease-free survival increases from less than 1% to 5 to 10% (15, 20).

Complete regression of all signs of disease during therapy is, however, followed by relapse and death in 70 to 80% of the cases, presumably due to minute fractions of resistant cells either existing prior to or arising during chemotherapy (26). The major therapeutic progress which characterizes the step from single agent to 4-agent chemotherapy in SCC is, perhaps, clinical proof of the heterogeneity of this tumor (13, 25). Simultaneous administration of more than 4 agents is not possible due to their toxicity. New agents are needed to overcome cellular resistance, but the results of current Phase II trials have not been promising (14). Eight to 10 active agents are available, however, and different combinations, schedules, and dosages permit various treatment policies, of which cyclic alternation between non-cross-resistant combinations is one possibility. In the chemotherapy of Hodgkin’s disease, this strategy has resulted in a significant improvement in overall survival (24).

The present study was a controlled randomized trial investigating this principle in patients with advanced SCC of the lung.

MATERIALS AND METHODS

All patients with SCC of the lung referred to the Finsen Institute or Bispebjerg Hospital in Copenhagen or to Renstromska Hospital in Gothenburg from August 1976 to April 1978 were included in the study, provided that: (a) the diagnosis of SCC was histologically or cytologically verified; (b) the patient was not older than 70 years; (c) the patient had extensive disease according to the Veterans Administration classification (11) (with the exception that metastases to the contralateral supraclavicular nodes were not regarded as constituting extensive disease); (d) no previous chemo- or radiotherapy had been given; and (e) informed consent was obtained.

The staging procedures were in accordance with the principles recommended by the International Association for the Study of Lung Cancer (22). They included general physical examination, chest X-ray, bilateral iliac crest biopsies, and aspirations and peritoneoscopy with liver biopsy (6). Histological or cytological examinations were applied whenever pleural, cutaneous, or lymph node involvement was suspected. Examinations for central nervous system metastases were only performed in suspected cases.

Complete blood count, concentrations of serum electrolytes, serum creatinine, serum lactate dehydrogenase, serum glutamic oxaloacetic transaminase, and serum alkaline phosphatase were obtained from all patients.

Histological evaluation was performed in accordance with the WHO classification (28) by the pulmonary pathologists at the respective hospitals.

Treatment. Following staging, all patients were stratified for performance status (27) and randomized to receive Regimen A (see below) continuously until progression of disease, when B was instituted, or to receive A alternating with B. Radiotherapy was applied for treatment of CNS metastases or for specific palliation in chemoresistant cases.

The 2 regimens (A and B) were: Regimen A, 1-(2-chloroethyl-3-cyclohexyl-1-nitrosourea, 70 mg/sq m p.o., cyclophosphamide, 1000 mg/sq m i.v., and vincristine, 1.3 mg/sq m i.v. (maximally 2 mg) on Day 1 and methotrexate, 20 mg/sq m p.o. on Days 15 and 18. The cycle time was 4 weeks. Vincristine was administered weekly the first 4 weeks; and Regimen B, doxorubicin, 30 mg/sq m i.v. on Day 1 and VP-16-213 (kindly supplied by Sandoz, Ltd., Basel, Switzerland), 100 mg/sq m p.o. on Day 14, with cycles repeated every 28 days. All patients received VP-16-213, 4’-demethylepipodophyllotoxin 9-[4,6-C-(R)-ethylidene-β-D-glucopyranoside] and doxorubicin at progression of disease or a regimen of (a) alternating with (b). Seventy-six patients received the continuous regimen; 70 patients received alternating treatment. Response rates were 68 and 72%, respectively. The median duration of response was 16 weeks in patients receiving continuous treatment compared to 28 weeks in patients receiving alternating treatment (p < 0.05). No survival time difference was observed between the groups, median survival being 36 and 38 weeks, respectively. Four patients became long-term survivors (5.6+, 5.5+, 5.1, and 4.7+ years). All received alternating therapy. Six toxic deaths were observed among patients receiving continuous therapy compared to only one death among those in the alternating regimen. In conclusion, alternating combination chemotherapy leads to prolonged duration of remission. Duration of survival is not prolonged in uncured patients, but an increased possibility of long-term disease-free survival cannot be precluded.
on Days 1, 2, 3, and 4. The cycle time was 3 weeks. Dosages were increased by 33% if the blood counts remained within normal limits but were reduced 33% if the WBC was between 2,000 and 3,000/cu mm or if the platelet counts were 75,000 to 100,000/cu mm. Treatment was withheld if the WBC was less than 2,000/cu mm or the platelet count was less than 75,000/cu mm.

The patients were scheduled to leave the hospital on Day 2 after initiation of therapy and then to remain as outpatients for as long as possible.

Therapy was continued until progression of disease was documented or for 18 months, when reevaluation was performed. This included bone marrow examination, peritoneoscopy with liver biopsy, and bronchoscopy.

Evaluation of Response. Evaluation of response followed the WHO recommendations (27), with the exception that duration of response was counted from observation of response to progression. Bone marrow involvement and clinically “silent” liver metastases were not evaluable parameters. Evaluation of response depended, therefore, upon radiological chest lesions and superficial metastases, which were examined at least every 4 weeks. All chest X-rays have been evaluated retrospectively by 2 of the authors to obtain as consistent and precise a determination of disease progression as possible. According to the definitions (27), a response must last at least 4 weeks. Patients dying within this period were regarded as having “progressive disease” if they died from lung cancer but were regarded as unevaluable if they died from toxicity or from an unrelated cause.

Statistical analysis included t tests or Wilcoxon analyses, depending on the observed distribution of data (3). \( x^2 \) tests were applied for comparison of proportions, and survival data were examined by use of life tables and log rank tests (23). \( p < 0.05 \) was regarded as significant.

RESULTS

A total of 150 patients were entered into the study: 105 at the Finsen Institute; 18 at Bispebjerg Hospital; and 27 at Renstroem-Ska Hospital. Four patients were excluded because the histological diagnosis was changed at pathological reclassification, leaving 146 eligible patients.

The principal prognostic features (21) for the 2 treatment groups are summarized in Table 1. No statistically significant differences were observed. The median time from diagnosis to initiation of chemotherapy was 15 days for both groups.

Antitumor Effect. The survival curves for the 2 treatment groups are shown in Chart 1. No significant difference was observed. The median duration of survival was 36 weeks or 38 weeks for patients receiving the continuous or the alternating regimen, respectively. No significant differences were observed when survival data for patients in the various response categories in the respective treatment groups were compared (Table 2 and Chart 2).

Sixty-six patients receiving the continuous regimen and 64 patients receiving the alternating regimen were evaluable for response. Early death was responsible for 3 unevaluable cases in the continuous group and for 1 such case in the alternating group. In the continuous group, 2 patients died from sepsis while granulocytopenic, and the third died from pulmonary embolism. Cardiac arrest due to ventricular arrhythmia caused one early death in the alternating group. The remaining 7 patients in the continuous group and 5 patients in the alternating group had no evaluable lesions.

The response rates for the 2 regimens were 68 and 72%, respectively (Table 2). Complete remissions were observed in 17 and 23% of the patients receiving the continuous regimen and the alternating regimen, respectively \((p > 0.15)\). Response durations are depicted as life tables in Chart 3. The difference between the curves is statistically significant \((0.01 > p > 0.005)\). The median duration values for the 2 regimens are 16 weeks and 28 weeks, respectively.

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### Table 1

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of patients</th>
<th>Sex (F) (%)</th>
<th>Median age (yr)</th>
<th>Performance status (%)</th>
<th>No. of distant sites (%)</th>
<th>Metastatic pattern (%)</th>
<th>SGOT* (%)</th>
<th>LDH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous</td>
<td>76</td>
<td>29</td>
<td>61</td>
<td>0-1 3-4 1 site 2 sites 3 sites</td>
<td>Pleura, trachea, or contralateral site Bone/marrow Liver CNS Skin/distant lymph node</td>
<td>≤ upper limit ≤ 2 times upper limit</td>
<td>67 16 9 22 40 21 33 24 8 21</td>
<td>74 92 50 75</td>
</tr>
<tr>
<td>Altering</td>
<td>70</td>
<td>26</td>
<td>61 (42-69)*</td>
<td>0-1 3-4 1 site 2 sites 3 sites</td>
<td>Pleura, trachea, or contralateral site Bone/marrow Liver CNS Skin/distant lymph node</td>
<td>≤ upper limit ≤ 2 times upper limit</td>
<td>64 17 7 34 30 5 34 33 1 24</td>
<td>67 87 51 74</td>
</tr>
</tbody>
</table>

* SGOT, serum glutamic oxaloacetic transaminase; LDH, lactate dehydrogenase.

* Numbers in parentheses, range.
Table 2

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Eligible patients</th>
<th>All patients</th>
<th>Complete response</th>
<th>Partial response</th>
<th>Non-responders</th>
<th>Evaluable patients</th>
<th>Responding patients</th>
<th>Complete response</th>
<th>Non-change patients</th>
<th>Median response duration (wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous</td>
<td>76</td>
<td>36</td>
<td>54(^a)</td>
<td>44(^b)</td>
<td>14(^c)</td>
<td>66</td>
<td>45 (68(^c))</td>
<td>11 (17)</td>
<td>4</td>
<td>16(^d)</td>
</tr>
<tr>
<td>Alternating</td>
<td>70</td>
<td>38</td>
<td>80(^a)</td>
<td>40(^b)</td>
<td>26(^a)</td>
<td>64</td>
<td>46 (72)</td>
<td>15 (23)</td>
<td>10</td>
<td>25(^d)</td>
</tr>
</tbody>
</table>

\(^a\) Result of log rank test, \(p = 0.17\).
\(^b\) Result of log rank test, \(p > 0.50\).
\(^c\) Numbers in parentheses, percentage.
\(^d\) Result of log rank test, \(p < 0.01\).

Long-Term Survival. Ten patients, 5 patients from each of the treatment groups, were without overt signs of disease after 18 months of chemotherapy. At peritoneoscopy, liver metastases were observed in one of the patients from the continuous group, while restaging confirmed disease-free status in the other 9 patients.

The remaining 4 long-term survivors from the continuous group have died from relapse of SCC (Table 3). One patient from the alternating group died from a squamous cell carcinoma in the contralateral lung 3.5 years after restaging. Relapses from SCC have been observed in 2 patients in this group. In one of them, relapse was restricted to the mediastinal glands, and the patient is alive and free of disease 2.1 years after mediastinal irradiation. The last 2 patients are clinically free of disease 5.6 and 5.7 years after initiation of alternating chemotherapy.

The obvious "cure rates" thus are 0 of 76 and 4 of 70 for the continuous and alternating groups, respectively, corresponding to 95% confidence intervals of 0 to 5% and 2 to 14%. The figures seem too small, however, to justify testing of significance.

Treatment Characteristics. Reductions or protractions of drug dosages were necessary in all patients. The cumulative total dose received declined gradually as time went on, having begun at a theoretical 100% value. After 1 year of chemotherapy, patients in the continuous group had received 50 to 60% of the scheduled accumulated doses, which was less than the 60 to 70% received by patients treated with the alternating regimen.

Therapy with Regimen B was initiated in 49 patients subsequent to progression on Regimen A. The remaining 27 patients had either expired due to rapid progression of the cancer or been removed from treatment because their general condition was inadequate for further chemotherapy. Eight of the 49 patients lacked evaluable lesions, one patient was lost to follow-up, and one patient died from progressing CNS metastases during the first cycle. Among the 39 evaluable patients, 4 partial remissions were observed, resulting in a response rate of 10%. The durations of these remissions were 59, 63, 95, and 147 days. Because of rapid progression of disease, a majority of the patients only received 2 cycles of the 2-agent regimen.

Among patients on the alternating regimen, 16 received further chemotherapy with investigative agents in Phase II trials. Cranial or spinal irradiation because of CNS involvement was received by 14 patients in the continuous group and by 6 patients on the alternating regimen.
in the alternating group. In the respective groups, 5 and one of these patients presented with CNS metastases at time of diagnosis. At postmortem examination, brain metastases were observed in 13 of 28 patients from the continuous group and in 12 of 26 patients from the alternating group. Palliative irradiation of the lung tumor and the mediastinum was given to 15 patients from each of the 2 treatment groups. Postmortem examinations were performed in 37 patients and 35 patients from the continuous and alternating treatment groups, respectively. The histological diagnosis of SCC was confirmed in all cases. No differences were observed in the postmortem metastatic patterns when patients from the 2 treatment groups were compared.

Toxicity. The main toxicity was bone marrow suppression. Grade 4 toxicity (27) was observed in 23 and 22% of the patients in the respective treatment groups. Febrile episodes during leukopenic periods leading to hospital admission and treatment with an intensive antibiotic regimen were observed in 10 patients in the continuous group and in 6 patients in the alternating group. Three patients and 1 patient, respectively, died during these episodes. Thrombocytopenia was observed in both treatment groups, as was a gradual decrease in the platelet counts during the 18 months of chemotherapy. Patients receiving the continuous regimen declined to an average platelet count of 130,000/cu mm compared to a level of 200,000/cu mm for patients treated with the alternating regimen. Three patients in the continuous group died from hemorrhage due to thrombocytopenia and methotrexate mucositis. No hemorrhagic deaths were observed in the alternating group.

Neurotoxicity due to vincristine was observed in 75% of the patients in both treatment groups.

The majority of the patients remained outpatients during Phase III chemotherapy. Apart from the 5 to 7 days' stay for staging, the average number of days in the hospital during Phase III therapy was 6.1 per patient in the continuous group and 6.2 per patient in the alternating group, i.e., 5 and 3%, respectively.

DISCUSSION

Two major assumptions must be validated before interpreting the results observed in this trial. All agents must be therapeutically active, and the applied combinations must be non-cross-resistant. Support for these assumptions can be derived from previous studies (13, 16, 17, 25). This study indicates that alternation between these 2 regimens did not help a larger proportion of patients, but sensitive tumors were controlled for a significantly longer period, and a slightly higher ratio of clinical complete remissions was observed. Long-term disease-free survival was only observed in patients receiving alternating therapy. The improved results were not associated with increased toxicity.

The tapering of dosage observed in this study corresponds to general clinical experience that maintenance treatment is less intensive than is treatment in the induction period. Maintaining the patient out of the hospital with a reasonable quality of life explains further dose reductions over and above those necessitated by bone marrow toxicity. The dose reductions were most pronounced in patients treated with the continuous regimen, and all 3 hemorrhagic deaths occurred in this group. This increased toxicity may partly be caused by the 4-weekly dosage of 1-(2-chloroethyl-3-cyclohexyl-1-nitrosourea. Another interpretation of the toxicity data may be that slightly higher doses of VP-16-213 and doxorubicin might have been tolerated.

A tendency to shorter duration of survival in nonresponding patients receiving the continuous regimen may partly be explained by the increased toxicity of this treatment, but a more likely explanation is the pronounced difference between the fractions of "no-change" patients in the 2 treatment groups. This difference is presumably due only to stochastic variation.

The low response rate in patients receiving Regimen B subsequent to progression on Regimen A obviously refutes the postulated non-cross-resistance between the 2 regimens. Inhibition of tumor growth due to therapy with VP-16-213 and doxorubicin is, however, the only reasonable explanation of why patients in the continuous group survived as long as did the patients in the alternating group.

The use of alternating non-cross-resistant chemotherapy has been tested by several groups. No interpretation of the efficacy of alternating therapy compared to continuous therapy can be made from the uncontrolled trial by Aroney et al. (4) or from studies by Broder et al. (5) and Lininger et al. (19), both of which compare 2 different alternating regimens. In all 3 studies, however, response rates and survival data were comparable to previous results with continuous regimens. Five trials comparing various schedules and combinations of non-cross-resistant agents with the continuous use of all or some of the same agents have led to various results. Patients who received alternating therapy survived significantly longer than did those without alternation in a trial by the Eastern Cooperative Oncology Group (9). However, no significant difference between the survival of patients given alternating treatment and the survival of those

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Initial disease</th>
<th>Relapse pattern</th>
<th>Total survival (wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous</td>
<td>Liver</td>
<td>Liver, bone marrow, pleura</td>
<td>114</td>
</tr>
<tr>
<td>Patient 1</td>
<td>Pleura</td>
<td>CNS, lymph nodes</td>
<td>132</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Liver, lymphatic glands</td>
<td>Liver</td>
<td>138</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Bone marrow</td>
<td>Liver, trachea</td>
<td>199</td>
</tr>
<tr>
<td>Alternating</td>
<td>Liver</td>
<td>Liver, lymph nodes, skin</td>
<td>102</td>
</tr>
<tr>
<td>Patient 1</td>
<td>Trachea</td>
<td>Mediastinum</td>
<td>248+</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Bone</td>
<td>Squamous carcinoma</td>
<td>266</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Bone</td>
<td>No relapse</td>
<td>290+</td>
</tr>
<tr>
<td>Patient 4</td>
<td>Liver, bone marrow</td>
<td>No relapse</td>
<td>295+</td>
</tr>
<tr>
<td>Patient 5</td>
<td>Liver</td>
<td>No relapse</td>
<td>295+</td>
</tr>
</tbody>
</table>
receiving continuous regimens was observed in other studies (1, 2, 6, 18). Data for a reliable comparison of response durations are not available. Inclusion of less active agents, according to current experience, may explain some of the diversity in these results. Patients who obtain remission in the induction period will obviously receive an active treatment if the same combination is continued. Randomization within this selected group of patients, which has been done in some of these trials, tends, therefore, to underestimate the efficacy of the alternating policy. Theoretical calculations based on a simple, heterogeneous tumor model suggest the superiority of therapeutic alternation between 2 non-cross-resistant combinations (10).

Few patients with small cell carcinoma of the lung are cured, especially if the disease is clinically disseminated at time of diagnosis. The observation in this trial of improved response durations in patients who received alternating chemotherapy should prompt further investigations of this treatment policy.

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REFERENCES

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