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Combined Modality Treatment of Short Duration in Small Cell Lung Cancer

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Abstract—*Fifty-seven patients with small cell lung cancer (SCLC) (limited disease = LD in 23, extensive disease = ED in 34) received the combination of CCNU, cyclophosphamide, vincristine and methotrexate (CCOM). A mean number of only 6 (range 1–17) courses of chemotherapy were given. All LD patients received consolidation locoregional radiation (30 Gy) after two courses of chemotherapy. A complete response (CR) was obtained in 61% of LD and 12% of ED patients, and a partial response in 22 and 35% respectively. Median survival was 54 and 34 weeks for LD and ED respectively. Five LD patients survived more than 2 yr, three of them remaining disease-free 4 yr after the cessation of treatment. A subset of 12 LD patients achieving a CR after two courses of chemotherapy was randomized to receive maintenance chemotherapy or observation only after the consolidation radiotherapy. In this small-sized randomized trial maintenance treatment showed a significant decrease of the patients' quality of survival compared to no maintenance treatment. We conclude that combined modality treatment of short duration proved effective in SCLC. Future randomized studies are necessary to show whether prolonged chemotherapy has a meaningful impact on survival, or otherwise the resulting morbidity will plead against it.*

INTRODUCTION

SMALL cell lung cancer (SCLC) pursues a rapid clinical course with a median survival in untreated patients of less than 3 months [1]. The course of the disease has been substantially modified by combination chemotherapy [2] and an objective response has been obtained in more than 75% of all patients [3]. However, the vast majority of patients with SCLC even after achieving a complete response (CR) ultimately relapse and die from the disease. Because of this the tendency has been to prolong chemotherapy even after the achievement of CR accepting the resulting morbidity. There are, however, insufficient data available about the optimal duration of chemotherapy in SCLC. Many SCLC patients in Europe are not treated with adequate chemotherapy because their physicians are not yet convinced of the net value to the majority of patients of one year of drug toxicity. If a short outpatient scheme proved as effective as the present 10- to 18-month protocols, it would be more readily used by a wider group of physicians in a larger group of patients.

The present paper reports the results of such a short scheme: a mean of only six courses were given, corresponding to about 4 months of treatment. In patients with limited disease (LD) the chemotherapy was combined with locoregional radiotherapy. In a subset of patients with LD we tried moreover to evaluate the impact of maintenance chemotherapy on survival and quality of life after the achievement of a CR. This part of the study involved a randomization into one of two arms: maintenance chemotherapy or observation only.

MATERIALS AND METHODS

From January 1978 to December 1980 all non-operable patients with histologically or cytologically proven SCLC referred to the Department of Pneumonology of the Leyden University Hospital were admitted to the study irrespective of

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age and performance status. The revised World Health Organization's classification [4] was used for the histologic typing. Routine staging included chest X-ray, mediastinal tomography, bronchoscopy, bone scan, unilateral bone marrow aspiration and biopsy, and an isotope brain scan. An isotope liver scan or ultrasound and a peritoneoscopy or percutaneous liver biopsy were performed if indicated. After staging the patients were classified as having either 'limited disease' (LD) or 'extensive disease' (ED), as defined by the VALG [5]. Performance status was graded according to the Karnofsky scale [6].

Chemotherapy for LD as well as ED consisted of the CCOM-scheme [2], including cyclophosphamide 1200 mg/m^2, vincristine 1.4 mg/m^2 (maximal dose 2.0 mg) and methotrexate 30 mg/m^2, all i.v. on day 1, repeated every 3 weeks. CCNU 80 mg/m^2 orally was added on day 1 of the odd courses. Patients with progressive disease were treated at their physician's discretion. A radiation dose of 30 Gy was given in 12 daily fractions over a 3-week period to all patients with LD after two courses of chemotherapy. Chemotherapy was withheld during radiotherapy. The target volume for radiotherapy included the primary tumour (extension prior to chemotherapy) and the drainage areas in the mediastinum. The ipsilateral supraclavicular fossa received iradiation only if involved. No prophylactic cranial irradiation was given. A subset of consenting patients with LD who achieved a CR after two courses of chemotherapy were randomized using the closed envelope method to receive maintenance chemotherapy or observation only after the completion of the consolidation locoregional radiotherapy.

Response criteria and grades of treatment toxicity were used as recommended by the WHO [7]. Patients who died within 6 weeks after the first course of chemotherapy were regarded as non-evaluable with respect to response unless progression of disease was documented within that period. Objective response was recorded mainly on chest films. For documentation of a CR at 2 yr after the cessation of treatment all original staging procedures including bronchoscopy were repeated. Survival and duration of response of all patients and of subgroups were described with Kaplan-Meier curves [8]. If appropriate, they were compared with the log rank test [9] and two-tailed P values were given.

RESULTS

Response and survival

A total of 57 patients entered the study. Their characteristics at the start of treatment are given in Table 1. Response to chemotherapy in patients with LD and ED is shown in Table 2. Responses were usually evident after two courses of chemotherapy. The survival curves of all 57 patients who entered the study, and of the patients with LD and ED separately, are displayed in Fig. 1. Note that patients who died before the results of treatment were evaluable are included in the analysis. The median survival for the whole group was 44 weeks (for LD 54 and for ED 34 weeks).

Table 1. Patients' characteristics at entry into the study

	Limited	Extensive	Total
No.	23	34	57
Age: mean	60.5	59.5	60.1
(range)	(36–73)	(43–78)	(36–78)
Sex: m	17	33	50
f	6	1	7
Karnofsky: mean	79	70	74
(range)	(10–100)	(20–100)	(10–100)

Table 2. Survival and response to chemotherapy

	Limited	Extensive	Total
No.	23	34	57
Complete response	14 (61%)	4 (12%)	18 (32%)
Partial response	5 (22%)	12 (35%)	17 (30%)
No change	2 (9%)	14 (44%)	16 (26%)
Progressive disease		1 (3%)	1 (2%)
Died before evaluation	2 (9%)	3 (9%)	5 (9%)
Median duration of response	42 weeks	23 weeks	32 weeks
Median survival	54 weeks	34 weeks	43 weeks

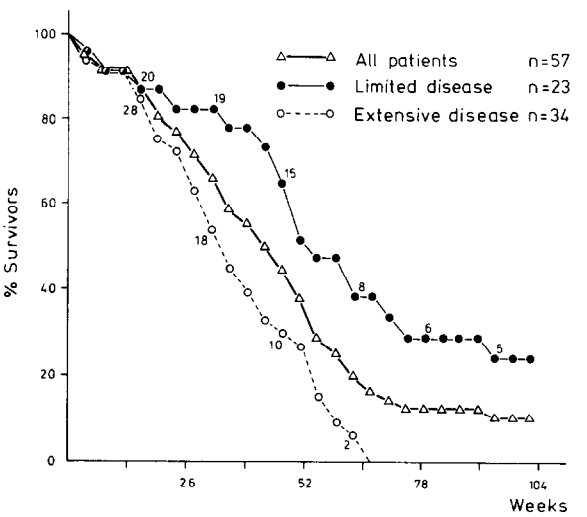

Fig. 1. Survival of all patients with small cell lung cancer, and of patients with limited and extensive disease separately. The number of patients remaining at risk is written along each graph. The difference between limited and extensive disease is statistically significant ($P < 0.01$).

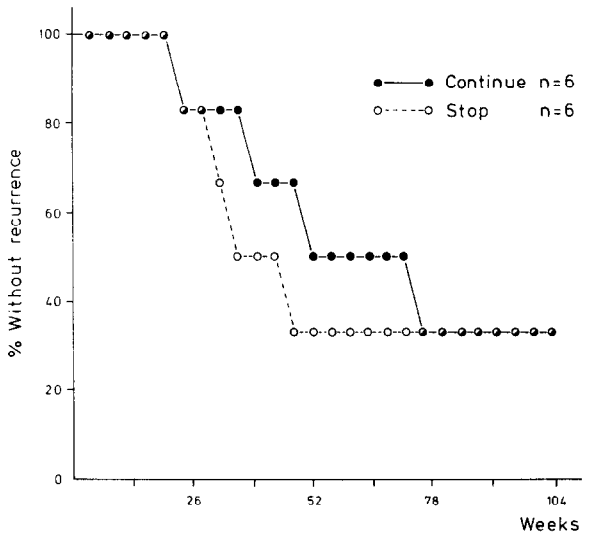

Fig. 2. Period of complete response in patients with limited disease achieving a CR after two courses of chemotherapy who were randomized to stop or to continue with chemotherapy after consolidation locoregional radiotherapy.

Five LD patients, four with CR and one with PR, survived more than 2 yr. Two of these CR patients received only two courses of chemotherapy plus radiotherapy, and two were randomized to continue chemotherapy after the same initial treatment. Three of the CR patients remained free of disease 4 yr aftr the cessation of treatment; the fourth CR and the PR patient died in the third year after progression of disease.

Twenty-one LD patients who were still alive after two courses of chemotherapy received locoregional radiotherapy. Nevertheless nine LD patients relapsed in the chest (eight within the radiated field).

In the subset of 12 LD patients achieving a CR who were randomized, because of small sample sizes, there were no statistical differences among the two treatment principles in survival or duration of response (see Fig. 2). Patients on maintenance treatment received a mean of 8.3 (range 5–15) courses of chemotherapy.

Toxicity, death and patients' acceptance

After the first course of chemotherapy severe leukopenia (leukocytes $<1.0 \times 10^9/l$) occurred in 20 patients, dictating a 25% dose reduction in the subsequent courses. In 18 patients only a moderate leukopenia (leukocytes $1–4 \times 10^9/l$) and in 19 patients no leukopenia (leukocytes $>4 \times 10^9/l$) was seen after the first course of chemotherapy. Toxicity after the second and subsequent courses of chemotherapy is displayed in Table 3. Dose modifications were mainly

Table 3. Number of patients with side-effects of the second and subsequent courses of chemotherapy

Side-effect	Grade 0	1	2	3
Nausea	2	23	19	8
Vomiting	24	12	11	5
Fatigue	33	8	2	8
Alopecia	6	20	20	5
Neurotoxicity	35	6	4	2
Constipation	42	4	5	1
Mucositis	42	3	5	
Leukopenia	25	17	6	

dictated by leukopenia. It was rarely necessary to delay an entire cycle for 1 week. Sixteen patients could not cope with chemotherapy and refused further treatment. This is elucidated in Fig. 3, which shows the other reasons to discontinue chemotherapy as well. Although patients with a good response were generally encouraged to

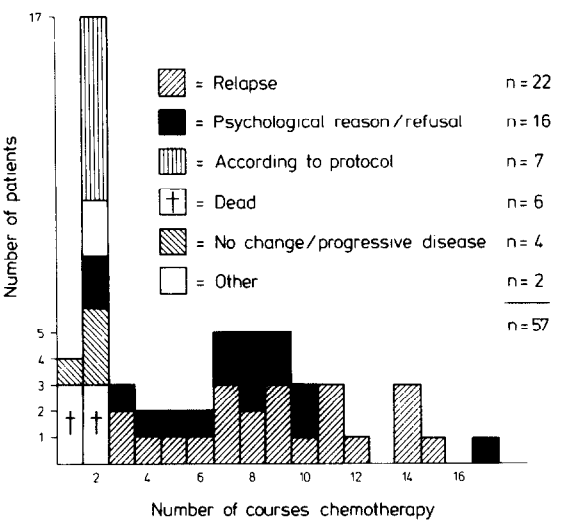

Fig. 3. Reasons to discontinue chemotherapy. The mean number of courses of chemotherapy is six.

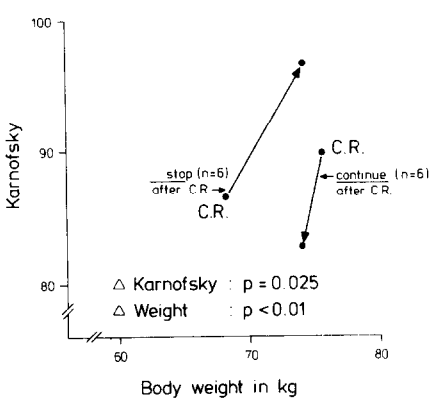

Fig. 4. Changes in mean body weight and performance status during the period of complete response (CR) in patients with limited disease achieving a CR after two courses of chemotherapy who were randomized to stop or to continue with chemotherapy after consolidation locoregional radiotherapy. For details see the text.

complete at least six courses of chemotherapy, no undue pressure was exercised to pursue treatment. This rather liberal approach led commonly to chemotherapy of short duration (mean for all patients six courses only). Two fatalities were partly attributable to the toxicity of the treatment, one dying from septicaemia, the other one from influenza. Another two patients died free of disease, one due to a myocardial infarction (no autopsy was performed). In the other patient CR was confirmed by autopsy 56 weeks after two courses of chemotherapy plus locoregional radiotherapy. In 49 patients death occurred after relapse and tumour growth was regarded as the cause of death.

Impact of maintenance chemotherapy on quality of life in limited disease

Patients with LD achieving a CR after two courses of chemotherapy who were randomized to stop treatment after the consolidation loco-regional radiotherapy showed an increase of their mean performance status and mean body weight during the period of CR (Fig. 4, arrow at the left-hand side). On the other hand, patients who continued chemotherapy after the same initial treatment did so at the cost of a decrease of mean performance status and mean body weight during the period of CR (Fig. 4, arrow at the right-hand side). The difference between these changes was significant at the $P = 0.025$ level for the change in performance and $P < 0.01$ for the change in body weight (Student's t test on paired observations). The duration of CR in the two groups was alike, as mentioned previously (see Fig. 2).

DISCUSSION

Although in the present study a mean number of only six courses of chemotherapy was given (corresponding to about 4 months of treatment), results were similar to those of representative studies with prolonged chemotherapy [2, 10–16] in terms of response rate, duration of response, median survival and long-term survival. This result warrants further studies addressing the issue of long vs short chemotherapy in a randomized fashion. Five patients (all with LD) survived more than 2 yr. This is a small number of patients, but remains an interesting result. The contribution of thoracic irradiation to this effect is not certain. The addition of radiotherapy to combination chemotherapy does not appear to improve median survival [17, 18]. However, whether the use of such a combined modality approach results in an increase in long-term survival remains to be seen [3, 19–21]. The dose and schedule of radiotherapy used in this protocol are apparently inadequate to prevent a relapse in the irradiated field, as was found in other studies [22, 23]. The usual toxicity of combination chemotherapy with or without radiotherapy was confirmed [24]. An appreciable number of patients (16 out of 57) could not cope with the chemotherapy and preferred to discontinue treatment. This reflects the patients' physical and psychological strain while on chemotherapy.

Maintenance treatment led to extra toxicity and caused a deterioration of the patients' well-being as measured by body weight and performance status (Fig. 4). It therefore requires justification to give maintenance therapy after a CR. We could not establish a positive effect of maintenance therapy on duration of response or on survival which might counterbalance the negative effects on the patients' well-being. Due to the small number of patients who were randomized to receive maintenance treatment or follow-up only, these results do not preclude even large differences in favour of any of the two treatment principles. In a CALGB study of different design [15], 36 out of 46 LD patients who achieved a CR were randomized and maintenance chemotherapy was found to prolong survival time. However, the results might easily have been biased by an uneven distribution of the different treatment modalities (four different chemotherapy regimens, some of which were inadequate by today's standards, all regimens with or without prophylactic brain irradiation) among the two arms (maintenance or observation only). In a more recent study involving 34 LD patients who were randomized after CR, any effectiveness of maintenance treatment could not be substantiated [25]. The issue therefore cannot be regarded as settled and further studies are needed to see whether maintenance therapy adds to survival. As a sequel to the present study a large-scale multicentre randomized trial addressing the issue of maintenance treatment has been initiated [26].

We conclude that a combined modality approach of short duration, as used in this study, proved effective in SCLC both in ED and LD. Maintenance chemotherapy caused a deterioration of the patients' quality of survival. Future studies will have to show whether prolonged chemotherapy has a meaningful impact on survival, or otherwise the resulting morbidity will plead against it.

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REFERENCES

1. Hyde L, Yee JM, Wilson RM, Patno ME. Cell type and the natural history of lung cancer. *JAMA* 1965, **193**, 140–142.
2. Hansen HH, Dombernovsky P, Hansen M, Hirsch F. Chemotherapy of advanced small-cell anaplastic carcinoma: superiority of a four-drug combination to a three-drug combination. *Ann Intern Med* 1978, **89**, 177–181.
3. Hansen HH. Management of small-cell anaplastic carcinoma, 1980–1982. In: Ishikawa S, Hayata Y, Suemasu K, eds. *Lung Cancer 1982*. Amsterdam, Excerpta Medica, 1982, 31–54.
4. Matthews MJ. Morphologic classification of bronchogenic carcinoma. *Cancer Chemother Rep* (*part* 3) 1973, **4**, 299–301.
5. Zelen M. Keynote address on biostatistics and data retrieval. *Cancer Chemother Rep* (*part* 3) 1973, **4**, 31–42.
6. Karnofsky DA, Abelmann WH, Craver L, Burchenal JH. The use of the nitrogen mustards in the palliative treatment of carcinoma, with particular reference to bronchogenic carcinoma. *Cancer* 1948, **1**, 634–656.
7. *WHO Handbook for Reporting Results of Cancer Treatment*. Geneva, World Health Organization, 1979, WHO Offset Publication No. 48.
8. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Statist Assoc* 1958, **53**, 457–481.
9. Peto R, Pike MC, Armitage P *et al.* Design and analysis of randomized clinical trials requiring prolonged observation of each patient: II analysis and examples. *Br J Cancer* 1977, **35**, 1–39.
10. Livingston RB, Moore TN, Heilbrun L *et al.* Small cell carcinoma of the lung: combined chemotherapy and radiation. A Southwest Oncology Group study. *Ann Intern Med* 1978, **88**, 194–199.
11. Lowenbraun S, Bartolucci A, Smalley RB *et al.* Southeastern Cancer Study Group. The superiority of combination chemotherapy over single agent chemotherapy in small cell lung carcinoma. *Cancer* 1979, **44**, 406–413.
12. Cohen MH, Ihde DC, Bunn PA *et al.* Cyclic alternating combination chemotherapy for small cell bronchogenic carcinoma. *Cancer Treat Rep* 1979, **63**, 163–170.
13. Ginsberg SJ, Comis RL, Gottlieb AJ. Longterm survivorship in small cell anaplastic lung carcinoma. *Cancer Treat Rep* 1979, **63**, 1347–1349.
14. Van Houtte P, Tancini G, De Jager R *et al.* Small cell carcinoma of the lung: a combined modality treatment. *Eur J Cancer* 1979, **15**, 1159–1165.
15. Maurer LH, Tulloch M, Weiss RB *et al.* A randomized combined modality trial in small cell carcinoma of the lung. *Cancer* 1980, **45**, 30–39.
16. Ettinger DS, Lagakos S. Phase III study of CCNU, cyclophosphamide, adriamycin, vincristine, and VP-16 in small cell carcinoma of the lung. *Cancer* 1982, **49**, 1544–1554.
17. Bunn PA, Ihde DC. Small cell bronchogenic carcinoma: a review of therapeutic results. In: Livingston RB, ed. *Lung Cancer*. The Hague, Martinus Nijhoff, 1981, Vol. I, 169–208.
18. Souhami RL, Spiro SG, Tobias JS, Geddes DM. Combination chemotherapy and radiotherapy in small cell carcinoma of the bronchus. World Conference on Lung Cancer, Tokyo, 1982, 213 (Abstr. III).
19. Bleehen NM, Bunn PA, Cox JD *et al.* Role of radiation therapy in small cell anaplastic carcinoma of the lung. *Cancer Treat Rep* 1983, **67**, 11–19.
20. Salazar OM, Creech RH. The state of the art toward defining the role of radiation therapy in the management of small cell bronchogenic carcinoma. *Int J Radiat Oncol Biol Phys* 1980, **6**, 1103–1117.
21. Comis RL. Small cell carcinoma of the lung. *Cancer Treat Rep* 1982, **9**, 237–258.
22. Cox JD, Byhardt RW, Wilson JF *et al.* Dose–time relationships and the local control of small cell carcinoma of the lung. *Radiology* 1978, **129**, 205–207.
23. Perez CA, Krauss S, Bartolucci AA *et al.* Southeastern Cancer Study Group. Thoracic and elective brain irradiation with concomitant or delayed multiagent chemotherapy in the treatment of localized small cell carcinoma of the lung. *Cancer* 1981, **47**, 2407–2413.
24. Feld R. Complications in the treatment of small cell carcinoma of the lung. *Cancer Treat Rev* 1981, **8**, 5–25.
25. Niederle N, Krischke W, Schulz U *et al.* Untersuchungen zur kurzzeitigen Induktions—und zyklischen Erhaltungstherapie beim inoperablen kleinzelligen Bronchialkarzinom. *Klin Wochenschr* 1982, **60**, 829–838.
26. Dutch Lung Cancer Study Group. Induction versus induction plus maintenance chemotherapy in small cell lung cancer. EORTC 1982, protocol 08825.