Eur J Cancer Clin Oncol, Vol. 17, No. 12, pp. 1249–1253, 1981.
Printed in Great Britain.

0277-5379/81/121249-05$02.00/0

Long-term Survival Five Years or More After Combination Chemotherapy and Radiotherapy for Small Cell Lung Carcinoma

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Abstract—*Five out of 42 patients with small cell carcinoma of lung, including 4 out of 17 initially presenting with limited desease (24%), remain alive and free of disease 5 years or more after combination chemotherapy (cyclophosphamide, vincristine, adriamycin, methotrexate and prednisolone) and radiotherapy. This represents a considerable improvement on previously reported results in the literature with radiotherapy or surgery alone. The use of combination chemotherapy in the treatment of small cell carcinoma of lung appears to increase significantly the chance of long-term survival and probable cure.*

INTRODUCTION

SMALL cell carcinoma of the lung has a very poor prognosis with a 5-yr survival after surgery or radiotherapy of 5% or less, even for patients presenting with clinically localised disease [1–4].

Combination chemotherapy has been shown to improve the outlook, at least in the short term. Such treatment achieves tumour regression in more than 70% of patients and significantly prolongs median survival compared with radiotherapy or with no treatment [5–8]. The long term benefits of combination chemotherapy are more controversial. A recent review of results from several centres reported a 2-yr disease-free survival of around 20% for patients initially presenting with limited disease [9]. However, little, if any, 5-yr survival data after chemotherapy appear to have been published and claims for long term survival and, perhaps, 'cure' achieved by chemotherapy have been treated with caution, and sometimes with scepticism [10].

Because of the obvious need for actual long-term survival data, we have re-analysed actual survival in 42 previously untreated patients who received combination chemotherapy and radiotherapy for small cell carcinoma of the lung between January 1974 and November 1975 (under the care of one of us, EDG), and for whom a minimum of 5-yr follow-up information is now available. Early results of treatment for some, but not all, of these patients have been previously reported [11].

MATERIALS AND METHODS

Patients

Forty-two previously untreated patients with histologically or cytologically proven small cell carcinoma of the lung were included in the study. Thirty-one were male and 11 female, with a median age of 64 yr (range 54–77 yr). Standard investigations used in their initial staging have been previously described [11]. Seventeen patients (40%) presented with disease limited to one hemithorax and ipsilateral supraclavicular nodes and the remaining 25 patients (60%) had extensive disease. Details are given in Table 1.

All patients were treated with the same combination chemotherapy regimen, using cyclophosphamide, 1 g i.v., vincristine, 1.5 mg iv., methotrexate, 200 mg by 24-hr infusion with folinic acid rescue, prednisolone, 40 mg i.v., and adriamycin, 40 mg/m^2 i.v. (COPAM), according to a schedule previously described in detail [11]. In general, chemotherapy was

Accepted 30 July 1981.
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Table 1. *Staging characteristics at initial presentation of* 42 *patients with small cell lung cancer*

	Extensive disease	Limited disease	Total
	25(60%)	17(40%)	42
Mediastinal involvement	20(80%)	12(70%)	32(76%)
SVC obstruction	4(16%)	2(12%)	6(14%)
Other nodes	12(48%)	1(6%)	13(31%)
Evidence of liver involvement	13(50%)	0	13(31%)
Marrow involvement	6(24%)	0	6(14%)
Bone involvement	4(16%)	0	4(10%)
Brain involvement	1(4%)	0	1(2%)
Inappropriate ADH	1(4%)	1(4%)	2(8%)
Inappropriate ACTH	2(8%)	0	2(5%)

repeated at 4-week intervals until both definite evidence of tumour recurrence and clinical deterioration occurred; in some patients, however, treatment was discontinued during remission because of toxicity or patient intolerance.

Thirty-nine of the 42 patients were also treated with local radiotherapy to a total dose of 3800–4500 rads over a 4-week period, either immediately prior to starting chemotherapy (14 patients) or after the first 2 courses (25 patients).

In this analysis all patients have been followed to death or for periods of at least 5 yr and actual, rather than actuarial, survival data are therefore presented. However, for statistical analysis of significance the actuarial method and log rank test of Peto *et al.* [12] were used.

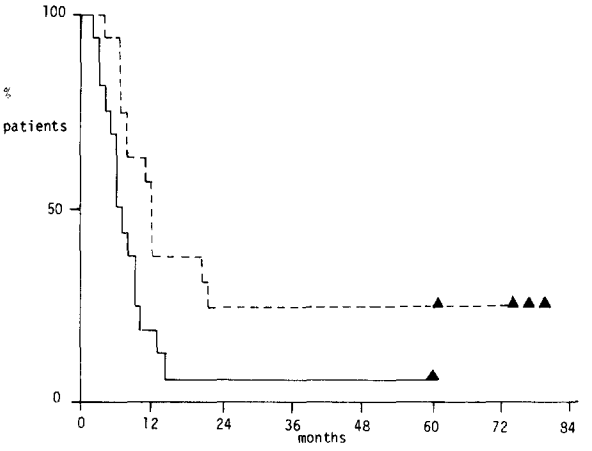

Fig. 1. *Duration of response to combination chemotherapy and radiotherapy (months).* (-------) *Patients with limited disease* (16); (———) *patients with extensive disease* (16); (▲) *patients still alive.*

RESULTS

Response to therapy

In the 17 patients presenting with limited disease, 10 achieved a complete response (59%) and 4 a partial response (24%), with an overall response rate of 82%. Two other patients initially treated with radiotherapy achieved a complete response prior to chemotherapy. In the 25 patients initially presenting with extensive disease, 3 (12%) achieved a complete response and 13 (52%) a partial response, with an overall response rate of 60%. Thus, out of the entire group of 42 patients, 30(71%) achieved a response, and 13 of these (31%) achieved a complete remission.

Duration of response

Response duration from the start of treatment is shown in Fig. 1. The median duration of response was 13 months for patients with limited disease and 6 months for those with extensive disease.

Survival

Actual survival data for the entire group of patients are shown in Fig. 2. The overall median survival was 10 months. Median survival for patients with limited disease was 13 months, compared to 7 months for those with extensive disease ($P = 0.02$). Median survival for responding patients was 14 months, compared with 5 months for non-responders ($P = 0.02$).

Long-term survival

Five of the original 42 patients (12%) remain alive and free of disease 5 yr or more after starting treatment (60, 60, 72, 74 and 78 months); these include 4 out of the 17 patients presenting with limited disease (24%) (95% confidence interval 4–44%). So far, no patient has relapsed after an interval of more than 23 months from the start of treatment.

Characteristics of these 5 long-term survivors are given in Table 2. Four presented with

limited disease, and one with extensive disease but restricted to contralateral supraclavicular lymph nodes. All 5 had radiological evidence of mediastinal lymphadenopathy at the time of diagnosis. Two presented with pleural effusions, one of which was demonstrated to contain malignant cells on cytology. No patients with liver, bone or marrow involvement achieved a long-term survival.

The 5 patients received, respectively, 21, 13, 8, 4 and 2 courses of chemotherapy; the latter 2 had this treatment discontinued because of intolerance or toxicity. All 5 also had radiotherapy, 3 immediately before chemotherapy and 2 after 2 courses of chemotherapy. One patient had a surgical lobectomy prior to starting chemotherapy and a second had an exploratory thoracotomy but without complete removal of tumour.

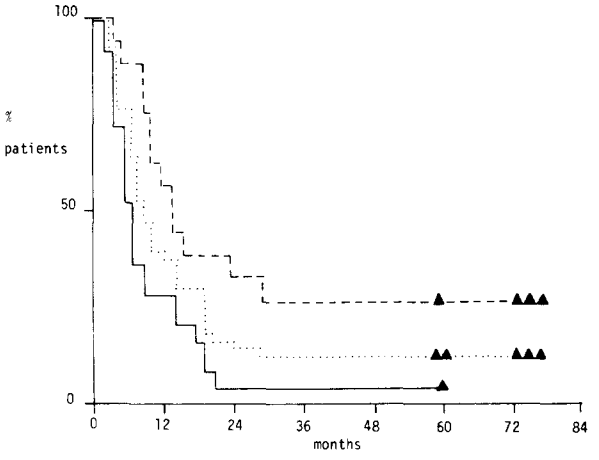

Fig. 2. Survival of patients treated with combination chemotherapy and radiotherapy (months). (--------) *Patients with limited disease* (17); (·····) *all patients* (42); (———) *patients with extensive disease* (25); (▲) *patients still alive.*

Toxicity

Details of toxicity with this treatment have been previously described [11]. The major problems were adriamycin-induced alopecia in all patients and nausea and vomiting in more than 50% of patients. Bone marrow suppression was not usually severe, with a mean white count nadir of 2700/mm^3 at 14 days.

DISCUSSION

Long-term survival after surgery or radiotherapy for small cell lung carcinoma is rare. Surgery is reported in most series to achieve a 5-yr survival of less than 2% overall and less than 5% even in patients presenting with apparently localised disease [2–4]. Radiotherapy has been shown in an MRC trial to achieve a longer median survival than surgery in patients with limited disease, but even in this 'good' prognostic group 5-yr survival after radiotherapy was only 5% [4]. These poor results have been confirmed in other studies [1, 3, 13].

Several trials have shown that chemotherapy prolongs median survival in this disease [5–8]. More recently, this form of treatment has also been claimed to increase long-term survival: individual studies have reported between 20 and 26% of patients with limited disease sur-

Table 2. Presenting features and treatment details of 5 long-term survivors (chemotherapy details in text)

Patient	Age	Sex	Extent of disease	Chemotherapy	Radiotherapy	Surgery	Survival (months)
(1) L.W.	58	M	Limited lung mediastinum pleura	13 Courses	4000 Rad	—	60 m
(2) C.H.	60	M	Limited lung mediastinum pleura	2 Courses	4300 Rad	Lobectomy	72 m
(3) P. O'B	56	M	Limited lung mediastinum	4 Courses	4000 Rad	Tumorectomy	74 m
(4) G. L.	63	M	Limited lung mediastinum	21 Courses	4100 Rad	—	78 m
(5) F. R.	64	M	Extensive lung mediastinum nodes	8 Courses	3500 Rad	—	60 m

viving 2 yr or more after chemotherapy, sometimes with added radiotherapy [14–16], but not always [17], and a review of 255 patients with limited disease from 10 centres found that 17% of patients remain alive and disease free 2 yr or more after chemotherapy [9]. These data have been interpreted optimistically by some as suggesting that chemotherapy has increased the chance of cure for this disease [16]. Until now, however, little, if any, 5-yr survival data after chemotherapy have been published, and because of this these optimistic claims have been criticised [10].

Our results are therefore of interest: they establish that a group of patients with small cell lung cancer (24% of those with limited disease) remain alive and free of disease 5 yr or more after treatment with combination chemotherapy and radiotherapy. It must be admitted that the study itself was a relatively small one, with a wide 95% confidence interval on the long-term survival rate (see Results), but other parameters, including overall response rate, complete remission rate, median duration of response and median duration of survival, are all similar to those reported elsewhere [9]. It is therefore unlikely that we have selected an atypical group and our findings support the claims of previous studies based on shorter follow-up that combination chemotherapy increases the chance of long-term survival and probable cure for patients with limited disease to more than 20%, a considerable improvement over results with local therapy alone.

In our study all but 2 of the patients who were going to relapse had done so within the first 20 months of diagnosis, and the longest time to relapse after starting treatment was 23 months. It may be that we were a little lucky here: occasional relapses have been reported 2 yr or more after starting chemotherapy [9, 18]. Nevertheless, these are uncommon, and it would appear that the long-term prognosis becomes very good for patients who remain free of disease for the first 24 months or so after treatment.

It would be very useful to be able to predict in advance which patients are most likely to achieve long term benefit from intensive combination chemotherapy. So far, we have been able to identify only 2 important prognostic factors. First, all 5 patients achieved a complete clinical remission on chemotherapy; this was not unexpected and has been confirmed in other studies as an essential pre-requisite for long-term survival [9]. Second, 4 of the 5 patients presented with limited stage disease, and the fifth had only one site of metastatic disease, in the contralateral supraclavicular lymph nodes. No long-term survivors were seen in patients with liver, bone marrow or osseous metastases. This confirms the findings of others: patients with extensive disease rarely achieve long-term survival with current forms of treatment [9]. We were unable to identify any characteristic histological features or sub-types of possible prognostic significance; although our numbers are obviously small, this finding is in keeping with a similar retrospective analysis from the National Cancer Institute [19].

Finally, our data do not allow us either to evaluate the role of radiotherapy or to predict the optimum duration of chemotherapy for maximum long-term benefit. All our patients received radiotherapy in addition to chemotherapy, as have most other patients so far reported in the literature as surviving 2 yr or more. However some 2-yr survivors have not received radiotherapy [9–17], and several control randomised trials have so far failed to show any improvement in *median* survival with the addition of radiotherapy to chemotherapy [20–22]. These early results need not necessarily reflect *long-term* survival, and follow-up data from these trials are clearly important. Likewise, 3 of our patients had between 8 and 21 monthly courses of chemotherapy and most published protocols currently advocate that treatment should be continued in responding patients for at least 12 months, and usually for longer. However, 2 of our long-term survivors received only 2 and 4 courses of chemotherapy respectively. It may well be that for some patients, a relatively short course of intensive combination chemotherapy in addition to adequate local treatment for bulk disease will prove as effective as prolonged maintenance chemotherapy for many months after remission has been obtained; trials are now required to investigate this.

REFERENCES

1. Broder LE, Cohen MH, Selawry OS. Treatment of bronchogenic carcinoma. II Small cell cancer. *Cancer Treat Rev* 1977; **4**: 219–260.
2. Fox W, Scadding JG. MRC Comparative trial of surgery and radiotherapy for primary treatment of small celled or oat celled carcinoma of bronchus. 10 year follow-up. *Lancet* 1973; **ii**: 63–65.

3. KATO Y, FERGUSON TB, BENNETT DE *et al.* Oat cell carcinoma of the lung. A review of 138 cases. *Cancer* 1969; **23:** 517–523.
4. MOUNTAIN CF. Clinical biology of small cell carcinoma: relationship to surgical therapy. *Semin Oncol* 1978; **5:** 272–279.
5. BERGSAGEL DE, JENKIN RDT, PRINGLE JF *et al.* Lung Cancer: clinical trial of radiotherapy alone V. Radiotherapy plus cyclophosphamide. *Cancer* 1972; **30:** 621–627.
6. GREEN RA, HUMPHREY E, CLOSE H *et al.* Alkylating agents in bronchogenic carcinoma. *Am J Med* 1969; **46:** 516–524.
7. KRAUSS S, PEREZ C. Treatment of localised undifferentiated small cell lung carcinoma with radiation therapy with or without combination chemotherapy with cyclophosphamide, adriamycin and DTIC. *Proc ASCO and AACR* 1979, 316.
8. MRC Lung Cancer Working Party. Radiotherapy alone or with chemotherapy in the treatment of small cell carcinoma of the lung. *Br J Cancer* 1979; **40:** 1–10.
9. GRECO FA, EINHORN LH, RICHARDSON RL *et al.* Small cell lung cancer: progress and perspectives. *Semin Oncol* 1978; **5:** 323–335.
10. Lancet Editorial. Small cell carcinoma of the bronchus—real progress is hard to come by. *Lancet* 1980; **i:** 77–78.
11. GILBY ED, BONDY PK, MORGAN RL *et al.* Combination chemotherapy for small cell carcinoma of the lung. *Cancer* 1977; **39:** 1959–1966.
12. PETO R, PIKE MC, ARMITAGE P *et al.* Design and analysis of randomised clinical trials requiring prolonged observation of each patient. II Analysis and examples. *Br J Cancer* 1977; **35:** 1–39.
13. MORGAN PGM. Small cell carcinoma of the lung. *Postgrad Med J* 1980; **56:** 162–165.
14. EINHORN LH, BOND WH, HORNBACK N *et al.* Long term results in combined modality treatment of small cell carcinoma of the lung. *Semin Oncol* 1978; **5:** 309–313.
15. MAURER LH, TULLOH M, WEISS RB *et al.* A randomised combined modality trial in small cell carcinoma of lung. *Cancer* 1980; **45:** 30–39.
16. OLDHAM RK, GRECO FA. Small cell lung cancer. A curable disease. *Cancer Chem Pharmacol* 1980; **4:** 173–177.
17. ISRAEL L, DEPIERRE A, CHOFFEL C *et al.* Immunotherapy in 34 cases of oat cell carcinoma of the lung, with 19 complete responses. *Cancer Treat Rep* 1977; **61:** 343–347.
18. HANSEN M, HANSEN HH, DOMBERNOVSKY P. Long term survival in small cell carcinoma of the lung. *J Am Med Assoc* 1980; **244;** 247–250.
19. MATTHEWS MJ, ROSENCWEIG M, STAGNET MJ *et al.* Long term survivors with small cell carcinoma of the lung. *Eur J Cancer* 1980; **16:** 527–531.
20. HANSEN HH, DOMBERNOVSKY P, HANSEN HS *et al.* Chemotherapy versus chemotherapy plus radiotherapy in regional small cell carcinoma of the lung. *Proc AACR and ASCO* 1979; **20:** 277.
21. STEVENS E, EINHORN L, ROHN R. Treatment of limited small cell lung cancer. *Proc Am Assoc Cancer Res* 1979; **20:** 435.
22. WILLIAMS C, ALEXANDER M, GLATSTEIN EJ *et al.* Role of radiotherapy in combination with chemotherapy in extensive carcinoma of the lung. *Cancer Treat Rep* 1977; **16:** 1427–1431.