Acta Oncologica 29 (1990) Fasc. 4

FROM THE DEPARTMENT OF CLINICAL ONCOLOGY, UNIVERSITY OF ANCONA, ANCONA, AND THE DEPARTMENT OF PNEUMOLOGY, HOSPITAL OF PESARO, PESARO, ITALY.

INDUCTION CHEMO-RADIOTHERAPY AND MAINTENANCE ALTERNATING CHEMOTHERAPY FOR SMALL CELL LUNG CANCER

D. TUMMARELLO, F. GUIDI, U. TORRESI, P. ISIDORI, A. ROSSI, C. DAZZI and R. CELLERINO

Abstract

Seventy-four patients with small cell lung cancer (SCLC) entered a program consisting of induction with three courses of CAV (cyclophosphamide, doxorubicin and vincristine) in limited disease or two courses of CAV plus two courses of DDP-VP16 (cisplatin, etoposide) in extensive disease, followed by chest radiotherapy (45 Gy) and prophylactic brain irradiation (30 Gy) in responsive patients. Subsequently, patients with response or stable disease received maintenance therapy by alternating courses of CAV, DDP-VP16 and C'MP (CCNU, methotrexate, procarbazine) during 1 year or until relapse. Sixty-seven patients were evaluable. Among 24 patients with limited disease 7/23 (30%) showed complete response, 15/23 (65%) partial response and 1/23 (5%) stable disease. Among 50 patients with extensive disease 1/44 (2%) showed complete response, 21/44 (48%) partial response, 13/44 (30%) stable disease and 9/44 (20%) progressive disease. Actuarial median survival in all patients was 8 months, in responders 11 months, and in failures (stable plus progressive patients) 4 months. Median survival was 11 months in limited disease patients and 7 months in extensive disease patients. Six patients became long-term survivors (8%). Despite the maintenance therapy with three different alternating chemotherapy regimens, our results were not superior to those obtained by more conventional chemotherapy.

Key words: Small cell lung cancer, chemo-radiotherapy, maintenance chemotherapy.

Current treatment programs for small cell lung cancer (SCLC) have resulted in 20–40% of complete response and a median survival of about 6 months in patients with extensive disease and 40–80% of complete response and a median survival of about 12 months in patients with limited disease (1–3).

However, only 10–15% of the patients survive longer than 2 years and real long-term survival and possible cure occur only exceptionally (4, 5).

During the last few years numerous new therapeutic approaches have been studied but none of them has yet led to significant improvement in response rate and survival.

In order to examine whether a more intensive chemo-radiotherapeutic regimen, including maintenance therapy with alternating courses including multiple partly non-cross resistant drugs, might possibly improve the results, we started the present study in January 1983.

We now report preliminary results following 57 months of observation.

Material and Methods

From January 1983 to October 1987, 78 patients with histologically or cytologically proven SCLC were admitted at the Department of Clinical Oncology, University of Ancona, and at the Department of Pneumology, Hospital of Pesaro. Prerequisites for inclusion in the study were: age less than 75 years, Karnofsky > 50, no prior treatment and measurable or evaluable disease. Before treatment the patients underwent physical examination, complete blood cell count, routine blood chemistry, chest radiography, bronchoscopy, radionuclide liver and bone scans, liver sonography, brain CT scan, and iliac crest bone biopsy. Limited disease (LD) was defined as tumor confined to one hemithorax, mediastinum and ipsilateral lymph nodes; spread beyond these limits was considered as extensive disease (ED) (6). The treatment program consisted of induction by three courses of CAV (cyclophosphamide 1 000 mg/m^2 i.v. day 1; doxorubicin 40 mg/m^2 i.v. day 1; vincristine 1.4 mg/m^2 i.v. day 1) every 3 weeks in LD

Accepted for publication 21 June 1989.

patients, and two courses of CAV and two courses of DDP-VP16 (cisplatin 40 mg/m^2 i.v. day 1 and etoposide 120 mg/m^2 i.v. days 2, 4, 6), every 3 weeks in ED patients. Complete responders (CR) and partial responders (PR) of both groups (LD and ED) then received continuous thoracic cobalt teletherapy, by opposed fields, to a midpoint dose of 45 Gy given in 24 fractions in 4 weeks and simultaneously prophylactic whole brain irradiation to a midpoint dose of 30 Gy in 18 fractions in 3 weeks.

Patients with further response or stable disease after the irradiation, then received maintenance therapy by alternating courses of CAV, DDP-VP16 and C'MP (CCNU 100 mg/m^2 per os day 1; methotrexate 30 mg/m^2 i.v. days 1, 7, 14, 21 and procarbazine 100 mg/m^2 per os daily from day 1 to day 14) cyclically administered every 3 weeks or with longer intervals if necessary for hematological recovery. This treatment was given for one year or until relapse.

The criteria for complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD), were those generally recommended (7). Response was evaluated when the induction chemo-radiotherapy was completed. Bronchobioptic confirmation was required to establish CR. The duration of response was measured from the time of objective tumor regression to progression. Survival was calculated from the start of treatment; actuarial survival curves were calculated according to the Kaplan-Meier method; the significance tests were assessed at 95% of confidence limits with alpha level = 0.05; the differences of significance were calculated by the log-rank test (8). Toxicity based on the WHO criteria (7) was registered, taking into account the number and the grade of toxic episodes in relation to the total of cycles administered. Myelosuppression was evaluated before the administration of each course and the drug doses were adjusted (or the treatment discontinued) according to the hematological or renal tolerance.

Results

Seventy-four patients entered the study. Median age was 60 years (range: 36–74) and male/female ratio 70/4. Twenty-four patients showed LD, 19 of whom had a Karnofsky status >70 and $5 \leqslant 70$; 50 patients showed ED, 27 of these had a Karnofsky status >70 and $23 \leqslant 70$. Sixty-seven patients were evaluable for response and toxicity; 4 were excluded since after the first course they refused further chemotherapy, due to drug related toxicity; the other 3 were early deaths.

Among 23 evaluable patients with LD, 7 (30%) had CR, 15 (65%) had PR and 1 had SD (5%). Among 44 evaluable patients with ED, 1 (2%) achieved CR, 21 (48%) PR, 13 (30%) SD and 9 (20%) PD. In all responsive patients (CR + PR) the median duration of response was 5 months (range 1+–48+). Main characteristics of patients and results of treatment are summarized in Table 1.

Table 1

Patients' characteristics and response to treatment

Characteristics	Patients with	
	limited disease	extensive disease
Eligible patients	24	50
M/F ratio	22/2	48/2
Median age in years (range)	60 (42–69)	60 (36–74)
Karnofsky		
>70	19	27
$\leqslant 70$	5	23
Treatment refusal	1	3
Early death	—	3
Fully evaluable patients	23	44
Response rates (%)		
Complete response	7(30)	1(2)
Partial response	15(65)	21(48)
Stable disease	1(5)	13(30)
Progression	—	9(20)
Median survival in months (range)	11 (3–48+)	7 (1–24)
Living patients (February 1989)	8	5
>8 months	4	2
$\leqslant 8$ months	4	3

Median survival in all patients was 8 months (1–48+), in responders 11 months (3+–48+) and in failures (SD + PD) 4 months (1–13). The Figure shows survival curves by extent of disease; patients with LD had a median survival of 11 months (3–48+) compared to 7 months (1–24) for patients with ED; this difference was significant ($p = 0.01$) when we considered the first 12 months of follow-up only.

At the time of writing (February 1989) 13 patients are still living. Six of them have achived 'long-term survival': 20.5, 21, 21.5, 24, 28+ and 48+ months respectively.

Among the 67 patients who started induction therapy, 49 underwent radiotherapy (23 with LD and 26 with ED) and, subsequently, 44 of them (21 with LD and 23 with ED) entered maintenance chemotherapy. These last mentioned patients received an average of 4 courses (1–8) of alternating combinations as stated in the protocol.

During this period, as a result of myelosuppression, drug doses were reduced in 35% of the CAV schedule and in 28% of the DDP-VP16 schedule. Concerning C'MP combination, owing to remarkable nausea and leukopenia, patients shortened the oral consumption of procarbazine from 14 to 7–10 days in about 30% of the cases.

The main observed toxic effects were hematological and gastrointestinal (nausea and vomiting). The toxic effects are reported in Table 2. On the whole the incidence of toxicity was similar to that commonly seen at cytotoxic treatment. No drug-related death was observed.

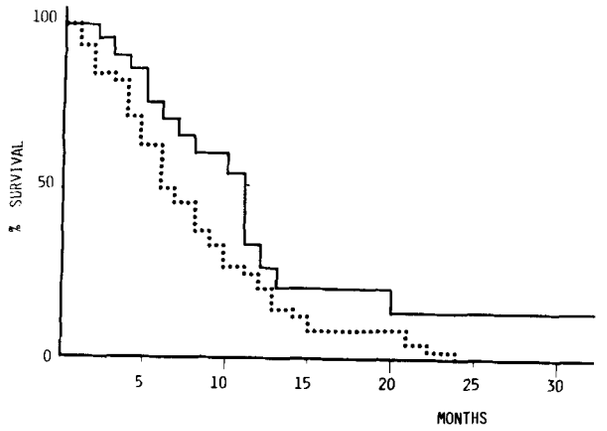

Figure. Actuarial survival curves (Kaplan-Meier) in patients with limited disease (——, n = 24) and extensive disease (· · · ·, n = 50).

Table 2

Toxicity of treatment

Toxic effects	WHO grading+			
	1	2	3	4
Hematological				
CAV	41*	28	26	—
DDP-VP16	13	12	16	3
C'MP	7	3	10	—
Gastrointestinal				
CAV	30	35	16	—
DDP-VP16	10	25	18	—
C'MP	4	12	11	2

+1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening.
*Number of courses with toxic episodes (total of courses administered: CAV = No. 215; DDP-VP16 = No. 80; C'MP = No. 34).

Discussion

The major therapeutic challenge in SCLC is the attainment and maintenance of complete response. Patients who achieve CR survive significantly longer than those who do not. A small fraction of those patients may become 'long-term survivors' and some of them might eventually be cured (5, 9, 10).

Over the past years many authors have raised questions about the role of intensive chemo-radiotherapy and of alternating non-cross resistant regimens (11, 12).

The present study is far less optimistic than other published reports (13, 14). Despite overall remission rates of 95% in LD and 50% in ED, we only recorded 7/23 complete remissions in the first group and 1/44 in the second group. The average duration of remission both in complete and in partial responders was only a few months and no obvious advantage was observed by the alternation of the three different schedules during maintenance therapy. Some authors using similar regimens have found higher complete response rates in patients with extensive disease and a median survival of about 10 months (15, 16). However, the majority of authors report median survival of LD patients between 11 and 14 months, and of ED patients between 6 and 8 months (17).

The survival rate obtained in our study is comparable to other large series. Livingston et al. (18) in their trial including 453 patients with extensive disease, reported a complete response rate of 16% and a median survival of about 7 months. The survival difference between most trials amounts to a few weeks only and, to our knowledge, no regimen has so far shown an obvious superiority. More or less favorable results may depend upon the character of the treated patients (performance status, weight loss, stage of disease, etc.) which can differ from series to series. For example, our series contained 4 females only and on average female patients seem to have a longer survival after treatment for SCLC then males (19). In addition, recent results of laboratory research have stressed the existence of particular properties inherent to the small cell type which may be of prognostic value. Such properties include expression of endocrine biomarkers and oncogenes responsible for drug or radiation resistance and may account for some of the observed variability in response rate to cytotoxic agents (20–22).

It is possible that in the future some of these prognostic factors may be taken into account and lead to the identification of subgroups, which may benefit from more intensive and individualized treatment. However, at present it seems unrealistic to believe that the overall results in SCLC could be essentially improved by combining available drugs.

Request for reprints: Dr Diego Tummarello, via Fornetto no. 57, I-60100 Ancona, Italy.

REFERENCES

1. Bergsagel D, Feld R. Small cell lung cancer is still a problem. J Clin Oncol 1984; 2: 1189–91.
2. Smyth JF, Hansen HH. Current status on research into small cell carcinoma of the lung: Summary of the Second Workshop of the International Association for the Study of Lung Cancer (IASLC). Eur J Cancer Clin Oncol 1985; 21: 1295–8.
3. Ihde DC. Current status of therapy for small cell carcinoma of the lung. Cancer 1984; 54: 2722–8.
4. Morstyn G, Ihde DC, Lichter AS. Small cell cancer 1973–1983: Early progress and recent obstacles. Int J Radiat Oncol Biol Phys 1984; 10: 515–49.
5. Aisner J, Alberto P, Bitran J, et al. Role of chemotherapy in small cell lung cancer: a consensus report of the International Association for the Study of Lung Cancer Workshop. Cancer Treat Rep 1983; 67: 37–43.
6. Zelen M. Keynote address on biostatistics and data retrieval. Cancer Chemother Rep 1973; 4: 31–42.
7. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981; 47: 207–14.

8. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SU. Design and analysis of randomized clinical trials requiring prolonged observations of each patients. II. Analysis and example. Br J Cancer 1977; 35: 1–39.
9. Seifter EJ, Ihde DC. Therapy of small cell lung cancer: a perspective on two decades of clinical research. Semin Oncol 1988; 3: 278–99.
10. Jacobs RH, Greenburg A, Bitran JD, et al. A 10-year experience with combined modality therapy for stage III small cell lung carcinoma. Cancer 1986; 58: 2177–84.
11. Abelof MD, Ettinger DS, Order SE, Khouri N, Mellits ED, Dorschel NT. Intensive induction chemotherapy for small cell carcinoma of the lung. Cancer Treat Rep 1981; 65: 639–46.
12. Choen MH, Ihde DC, Bunn Jr PA, et al. Cyclic alternating combination therapy for small cell bronchogenic carcinoma. Cancer Treat Rep 1979; 63: 163–70.
13. Evans WK, Shepherd FA, Feld R. VP-16 and cisplatin as first-line therapy for small cell lung cancer. J Clin Oncol 1985; 3: 1471–7.
14. Murray N, Sha HA, Brown E, Kostashuk E, Laukkanen E, Goldie J. Alternating chemotherapy and thoracic radiotherapy with concurrent cisplatin-etoposide for limited-stage small cell carcinoma of the lung. Semin Oncol 1986; (Suppl 3): 24–30.
15. Daniels JR, Chak LY, Sikic BI, Lockbaum P, Kohler M, Carter SK. Chemotherapy of small cell carcinoma of lung: A randomized comparison of alternating and sequential combination chemotherapy programs. J Clin Oncol 1984; 2: 1192–9.
16. Natale RB, Shan KB, Hilaris BS. Combination cyclophosphamide, adriamicin and VP-16 in treatment of small cell lung cancer. Am J Med 1985; 79: 303–8.
17. Hande KR, Des Prez RM. Current perspectives in small cell lung cancer. Chest 1984; 85: 669–77.
18. Livingston RB, Mira JG, Chew TT, Mc Gravan M, Costanzi JJ, Samson M. Combined modality treatment of extensive small cell lung cancer: A Southwest Oncology Group Study. J Clin Oncol 1984; 2: 585–90.
19. Evans WK, Feld R, Murray N, Willan A, Coy P, Osoba D. Superiority of alternating non-cross resistant chemotherapy in extensive small cell lung cancer. Ann Int Med 1987; 107: 451–8.
20. Johnson BE, Nau MM, Gadzar AF. Oncogene amplification of c-myc and n-myc in cell lines established from patients with small cell lung cancer is associated with shortened survival. Proc Am Soc Clin Oncol 1985; 4: 186.
21. Little CD, Nau MM, Carney DN, Gadzar AF, Minna JD. Amplification and expression of the c-myc oncogene in human lung cancer cell lines. Nature 1983; 306: 194–6.
22. Beck LK, Kane MA, Bunn Jr PA. Innovative and future approaches to small cell lung cancer treatment. Semin Oncol 1988; 3: 300–14.