Eur J Cancer Clin Oncol, Vol. 24, No. 3, pp. 519–526, 1988
Printed in Great Britain

0277–5379/88$3.00+0.00

Phase II Study of an Intensive Combination Chemotherapy with Cisplatin, Adriamycin, Etoposide and Cyclophosphamide (CAVE) in Small Cell Lung Cancer

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Abstract—*One hundred and twelve patients with small cell lung cancer (SCLC) were treated with a combination (CAVE) of cisplatin* (60 mg/m^2 *day* 1), *adriamycin* (45 mg/m^2 *day* 1), *etoposide* (80 mg/m^2 *days* 1-2-3) *and cyclophosphamide* (1 g/m^2 *day* 1) *given every* 4 *weeks. A total of* 10 *courses were given. Response evaluation was initially evaluated after the first two courses of CAVE and repeated at least after treatment completion. This regimen was associated with severe hematological toxicity, mainly leucopenia; five toxic deaths related to sepsis were observed. One hundred and one patients were evaluable for response:* 63 *with limited disease and* 49 *with extensive disease. Overall complete and partial response rates after the first two courses of chemotherapy were* 16% *and* 63% *respectively but* 14 *late complete responses were documented, leading to a* 30% *total complete response rate;* 38% *in patients with limited disease and* 19% *in those with disseminated disease. Median overall survival was* 46 *weeks with a* 17% 2 *year survival. The only significant prognostic factor for survival was the type of response. There was no survival difference between 'early' and 'late' complete responders. Complete responders had a* 75 *week median survival time with a* 34% 2 *year survival. CAVE is thus an effective regimen for SCLC, but with a considerable toxicity.*

INTRODUCTION

A HIGH rate of complete response and prolonged survival can be obtained by chemotherapy in small cell lung cancer (SCLC). Our first study conducted with a combination of cisplatin, adriamycin and etoposide [1] resulted in a high objective response rate (88% in limited disease and 81% in extensive disease, with respectively 64% and 23% complete responses) and in an overall median survival of 48 weeks. In our next study [2], we used the combination cyclophosphamide, adriamycin and etoposide with which Aisner *et al.* [3] reported some of the best results obtained in the treatment of SCLC with a very high response rate (90%) and impressive disease free long-term survival (30% at 2 years and 20% at 3 years in limited disease). However, with the same combination, Abeloff *et al.* [4] did not observe such good results (78% objective responses with 40% complete responses in limited disease and 18% in disseminated disease without disease free long-term survivors). In our study, we observed 82% objective responses in limited disease

Accepted 1 October 1987.
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and 66% in extensive disease with respectively only 20% and 7% of complete responses; overall and disease free 2 year survivals [5] were respectively 18% and 6% (24% and 9% for the patients with limited disease). Our results were thus intermediate between those obtained by Aisner *et al.* and Abeloff *et al.* as far as the response rates are concerned; however, the median survivals in all three studies were similar. Since possible synergism between cisplatin and etoposide has been suggested in experimental studies and in patients with small cell lung cancer [6–8], the addition of cisplatin to the adriamycin–cyclophosphamide–etoposide regimen was tested in a phase II trial in order to determine if this four-drug combination would increase the complete response rate in SCLC and the long-term survival.

Table 1. Patient characteristics

Eligible patients	112
Sex: M/F	103/9
Performance status:	
60	16
70	33
80	28
90	22
100	13
Loss of body weight:	
0%	49
1–5%	25
>5%	38
Median age (range) (years)	59 (37–74)
Limited disease	63
Disseminated disease	49
Evaluable lesions	73
Measurable lesions	39
Evaluable for response	101

MATERIALS AND METHODS

Criteria of eligibility to the study were the following: histological diagnosis of small cell lung cancer; no prior history of malignancy except non-melanomatous skin cancer and *in situ* carcinoma of the uterine cervix; no prior chemotherapy, radiation therapy or curative surgical resection; age <75 years; white blood cell and platelet counts respectively above 4000 and 150,000/mm^3; serum creatinine and bilirubin <1.5 mg/100 ml; no active cardiac disease (myocardial infarction within 4 months, angina pectoris, congestive heart failure); informed consent and accessibility for follow up.

Initial staging consisted of complete physical examination, evaluation of performance status (Karnofsky scale), chest X-ray with tomography or CT scan, bronchoscopy with biopsy, hematological counts, blood chemistries, ECG, bone scintigraphy, bone marrow biopsy, brain CT scan or isotopic scan and liver CT scan or echography. Limited disease (LD) was defined as a disease confined to the hemithorax, including bilateral supraclavicular nodes and homolateral pleural effusion. All other cases were considered as extensive disease (ED).

Therapy consisted of a total of 10 courses of a four-drug combination: cisplatin (60 mg/m^3 on day 1 with a short i.v. hydratation), adriamycin (45 mg/m^2 on day 1), etoposide (80 mg/m^2 on days 1–2–3) and cyclophosphamide (1 g/m^2 on day 1). Courses were repeated every 4 weeks if there was evidence of recovery from previous myelotoxicity (absolute granulocyte count >1500/mm^3 and platelet count >100,000/m^3). Prophylactic cotrimoxazole was prescribed during the period of myelosuppression. If granulocytopenia was <500/mm^3 or platelet nadir <50,000/mm^3, total doses of the drugs were reduced to 75% of the initial ones. Lack of recovery from myelosuppression on day 36 was a cause for removal from the study. A complete restaging with the same tests as initially was performed during the third course. Patients with complete response (CR) received prophylactic cranial irradiation (PCI) and seven further courses of CAVE. Those with limited disease and partial response (PR) were administered thoracic irradiation and PCI followed by seven courses of CAVE. All the other responders received a total of 10 courses of CAVE and, if a late CR was obtained, PCI. Twelve of the patients were included in a phase I study of late intensification with cyclophosphamide and etoposide after three induction courses with CAVE [9]. PCI consisted of a dose of 30 Gy delivered to the brain in 10 fractions over a period of 2 weeks. Chest irradiation was given to the primary site, the mediastinum and both supraclavicular nodes. A dose of 45 Gy was administered in 4 weeks with five fractions per week by parallel opposed fields from megavoltage equipment. The portals of irradiation included the initial lung tumor volume. Treatment of patients relapsing or failing to response was left to the discretion of the physician.

Patients were considered as evaluable for response if they completed two courses of treatment or if rapid progression of the disease or toxic death precluded the administration of the second course. In the latter cases, they were evaluated as failures. A complete remission (CR) consisted of disappearance of all known disease for a duration of at least 4 weeks. CR was called 'early' if it occurred after two courses and 'late' if it was obtained later. Partial remission (PR) of measurable disease consisted of a ≥50% decrease in a measurable lesion defined by the multiplication of the longest diameter by the greatest perpendicular one. In addition there could be no appearance of new lesions or progression of any lesions. The duration of the response needed to be at least 4 weeks. For evaluable disease, partial

Table 2. Hematological toxicity

		Leucocytes Definition	*n*	Platelets Definition	*n*
Number of evaluable cases (*n*)			72		68
Nadir grade	0	$\leq 4000/mm^3$	0	$\geq 100000/mm^3$	36
	I	3–3900	1	75–99000	10
	II	2–2900	17	50–74000	9
	III	1–2900	23	25–49000	9
	IV	<1000	31	<25000	4

response was an estimated decrease in a lesion size of 50% or more. No change was less than a 50% decrease in a total tumor size or than a 25% increase in the size of one or more measurable or evaluable lesions. Disease was considered progressive in the case of a 25% or more increase in the size of one or more measurable or evaluable lesions and/or of appearance of new lesions. All responses were evaluated during regular meetings of the group and by at least three physicians who did not belong to the institution of the investigator who took care that the patient WHO criteria were used to report toxicity.

Duration of response and survival were calculated from the first day of treatment. All eligible patients were considered as evaluable for survival. Survival curves were calculated by the method of Kaplan and Meier. The log-rank method was used to test the statistical significance of the difference between survival curves.

RESULTS

A total of 116 patients were included in the trial but four were ineligible: three because of wrong histology and one because of active cardiac disease. On the 112 eligible patients, 11 were not evaluable for response for the following reasons: drugs dose violation (1), absence of response evaluation (2), lost to follow up (3), treatment discontinued because of too high toxicity (3), treatment refusal (2). Table 1 shows the characteristics of the eligible patients; 63 presented with limited disease and 49 with extensive disease. Median Karnofsky performance status was 77.5 and median loss body weight 3.5%. Lesions were evaluable in 73 patients and measurable in 39. There were 103 men and nine women. The average total follow up period was 51 weeks. Study analysis was performed 18 months after registration of the last patient.

Toxicity was mainly hematological (Table 2). Severe leucopenia occurred in the majority of the patients: 75% has a leucocyte nadir of less than $2000/mm^3$ and 43% of less than $1000/mm^3$. Twenty-eight patients had an infection during treatment and five of these died with sepsis during the neutropenic period. Thrombopenia was generally moderate: bleeding was observed in two patients with grade II toxicity and successfully managed with transfusions. Alopecia was documented in almost all the patients as well as nausea and vomiting (usually grades II or III). Stomatitis occurred in 14 patients but was severe in only two. Mild diarrhea was observed in 1/3 of the cases. A grade II renal toxicity was documented. Dose reduction was performed in 32% of the patients and treatment courses were delayed in 30%.

Table 3. Response rate after two courses

	Overall	LD	ED
Total number of patients	112	63	49
Evaluable for response	101	58	43
Complete response	16	11	5
Partial response	63	39	24
Failure	16	7	9
Non-malignant early death	1	0	1
Toxic death	5	1	4

LD: limited disease; ED: extensive disease.

Table 4. Analysis of early (after two courses) and late (after more than two courses) complete responses

	Early CR	Late CR	Overall CR
n	16	14	30
LD	11	11	22
DD	5	3	8

As shown in Table 3 for the evaluation after the first two courses of chemotherapy, there were 16 complete responses (CR) and 63 partial responses (PR) among the 101 evaluable patients. In those with limited disease, CR was documented in 19% and PR in 67%. There was one toxic death (2%) while four were observed in patients with extensive disease (9%). In those, CR occurred in 12% of the cases and PR in 56%. Fourteen late complete responses were observed between the 3rd and 10th months of treatment (Table 4). All were evaluated as PR after the first two courses of chemotherapy.

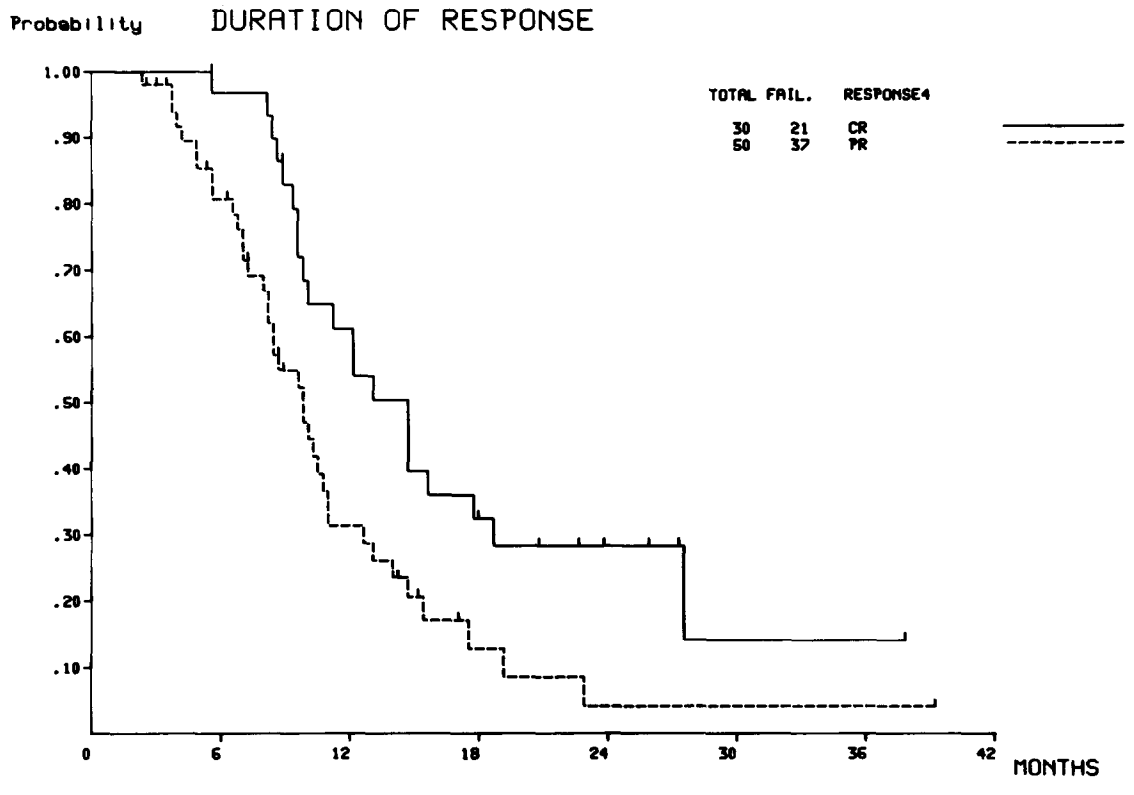

Fig. 1. Duration of response.

Four of these patients received a late intensification course with high doses of cyclophosphamide and etoposide and four others chest irradiation. Eleven of the late CR occurred in patients with limited disease and three in those with extensive disease. So the overall complete response rate was 30% with 38% (22/58) in limited disease and 19% (8/43) in extensive disease. One patient with no change at two courses became a partial responder after four courses of chemotherapy. If the definition of CR had been restricted to a normalization of the standard chest X-ray, our overall complete response rate would have increased to 38%. No prognostic factor was identified for response.

Overall median duration of response was 44 weeks. There was no difference between patients with limited disease (44 weeks) and those with extensive disease (42 weeks). Complete responders (median 56 weeks) had a significantly ($P = 0.006$) longer duration of response than partial responders (median 41 weeks) as shown in Fig. 1. Performance status, body weight loss, evaluability of the disease, age, sex or time of CR were not significant prognostic factors for the duration of response. In patients with limited disease, the initial site of relapse was local in 10, metastatic in 12 and local as well as metastatic in six of the patients whose site of progression was evaluated. Among the 35 patients with limited disease and treated by chest irradiation, local relapse was observed in eight cases. In patients with extensive disease, only a local relapse was observed in three, distant relapse in 15 and both in one. Of the 50 patients who had received prophylactic cerebral irradiation, four developed brain metastases. Of the 30 responders who had not received it, six had brain relapses.

As shown by Fig. 2, median overall survival was 46 weeks with a 17% 2 year survival. There was no significant survival difference (Fig. 3) between patients with limited disease (median 48 weeks) and those with extensive disease (median 41 weeks). Age, sex, loss of body weight, Karnofsky performance status and evaluability of the disease were not significant prognostic factors for survival. Complete responders had a 34% 2 year survival with a median survival time of 75 weeks while partial responders had a median survival time of 48 weeks with a 16% 2 year survival ($P = 0.03$). As shown in Fig. 4, there was no significant survival difference between early and late complete responders.

DISCUSSION

Despite the development of chemotherapy, long-term survival in patients with small cell lung cancer remains poor with about a 10% 2 year survival and a 5% 5-year survival [10–12]. The consensus report of the IASLC Workshop [13] suggested that optimal chemotherapy should induce more than 50% and 20% complete response rates for limited and extensive disease respectively, with median survival times of more than 14 and 7 months. A 3 year disease free survival of 15–20% should be obtained in

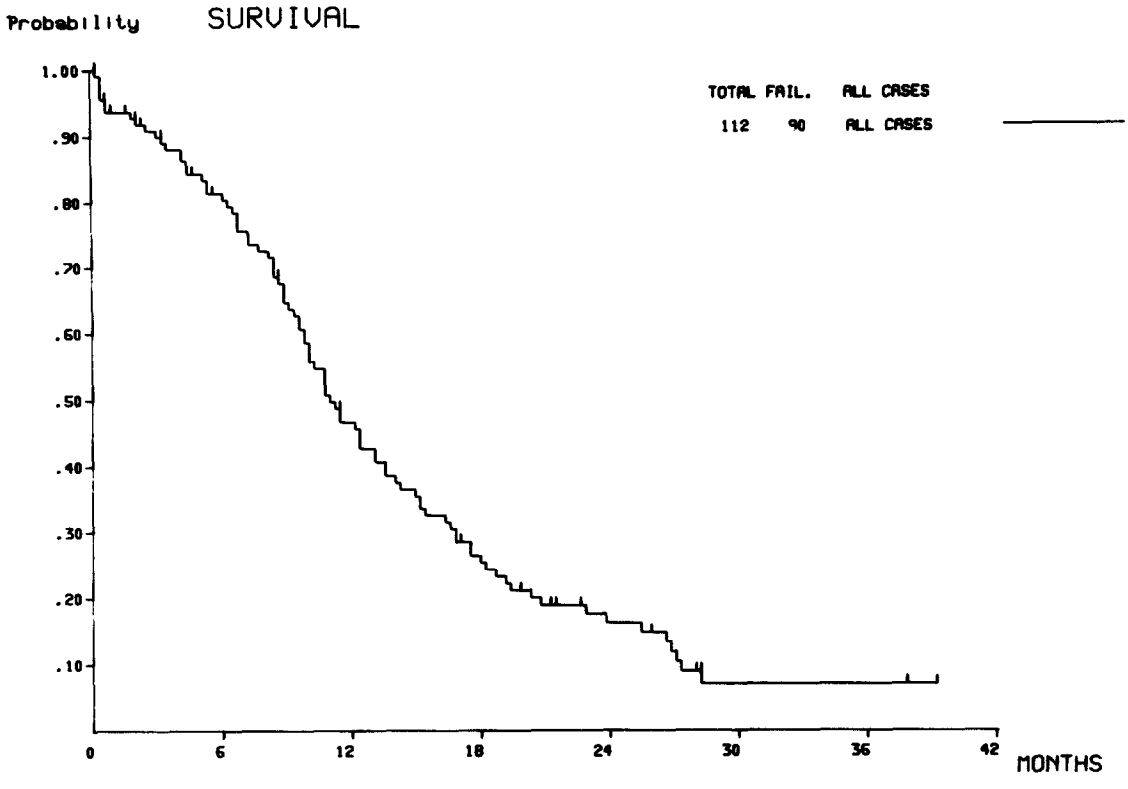

Fig. 2. Overall survival.

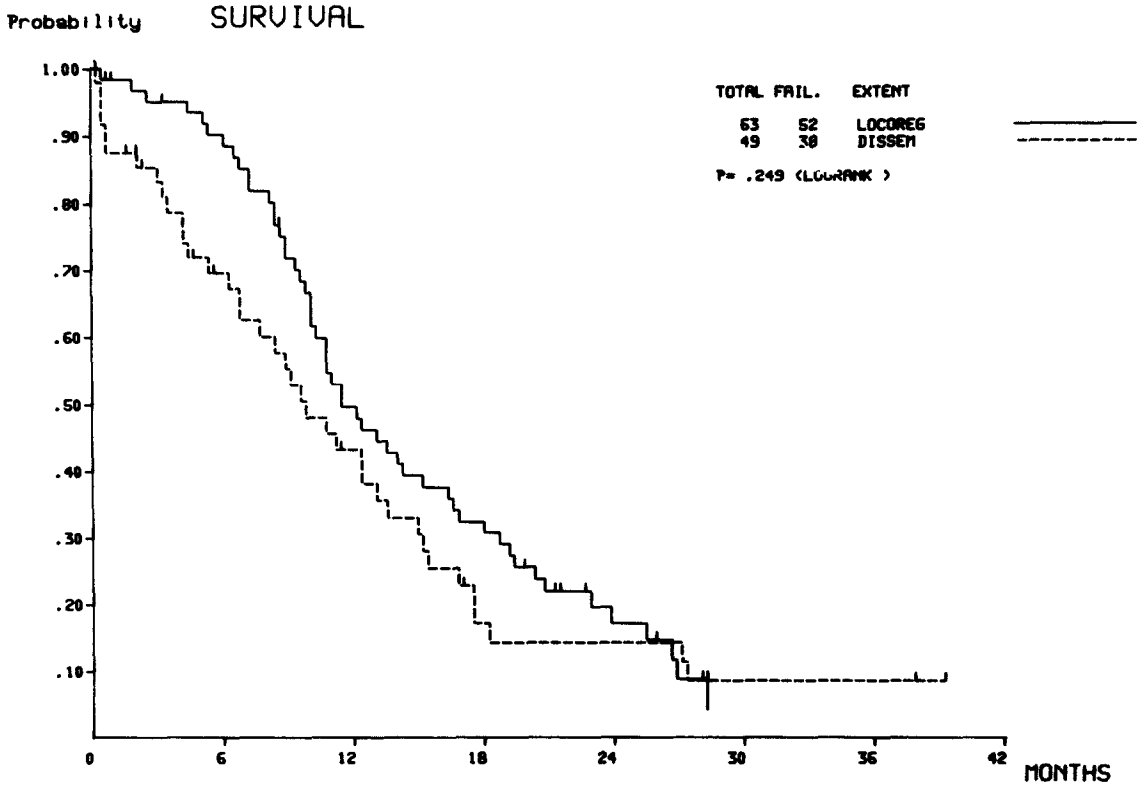

Fig. 3. Survival according to extent of disease.

patients with limited disease. Such results have been reported by Aisner *et al.* [14] with the intensive cyclophosphamide–adriamycin–etoposide regimen but were not confirmed by Abeloff *et al.* [4] or by our group [2]. A way to 'intensify' a chemotherapeutic regimen is to increase the number of drugs in the combination, as we have done in the present study by adding cisplatin to the above discussed regimen.

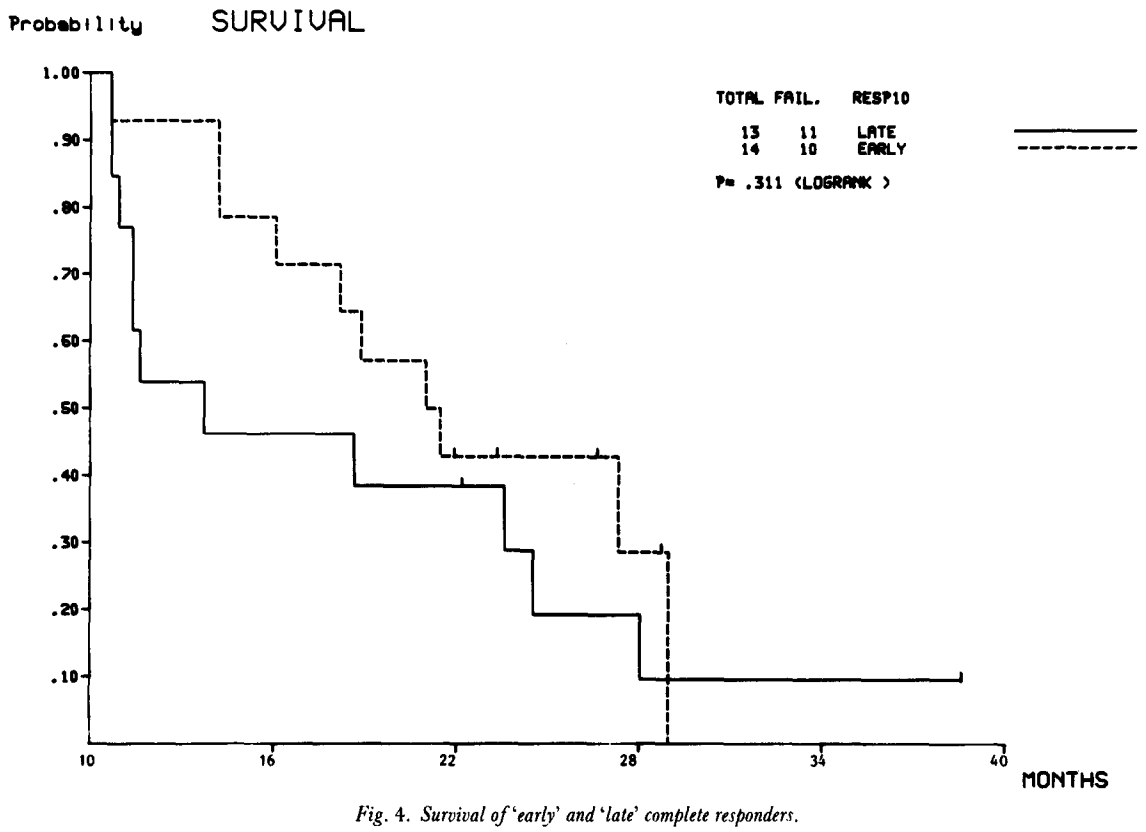

Fig. 4. Survival of 'early' and 'late' complete responders.

All drugs were given at full dosage. This unique schedule actually combined the two probably most active induction regimens for SCLC: adriamycin–cyclophosphamide–etoposide [14] and cisplatin–etoposide [6–8].

Our CAVE regimen resulted in an overall complete response rate of 30% (38% in limited disease and 19% in extensive disease). This relatively low figure could probably be explained partially by the maximized restaging procedures, including chest CT scan and fiberoptic bronchoscopy and by the systematic revaluation of the response during regular meetings of our cooperative group. If we only considered standard chest X-ray, our CR would have been 38%. Interestingly, about half of our complete responses were obtained only after the first two courses of chemotherapy, either by continuing the induction regimen or, in some cases, by the addition of chest irradiation or administration of a late intensification. There was no survival difference between 'early' and 'late' complete responders. The role of chest irradiation [15] or late intensification [16] administered in some of our patients probably does not explain the good survival of the late responders. Our data suggest thus that restaging for evaluation of complete responses should be repeated and that an intensive induction period should not be too short, i.e. not restricted to two courses of chemotherapy.

We observed 5% toxic deaths, because of septic complications occurring during the neutropenic period. These toxic deaths were mainly observed in patients with extensive disease. This rate is probably considered in the expected range of toxicity for such an intensive regimen [13].

Survival obtained in the patients treated with CAVE was analyzed after a minimal 18 months follow up period. Overall 2 year survival was 17%, a common figure for an intensive regimen. There was no significant survival difference between patients with limited and extensive disease. This observation was also reported by Markman *et al.* [17] with an intensive alternating chemotherapy. Other classical prognostic factors such as performance status or the loss of body weight [18–19] were also not significant for survival prediction in our study. The intensive induction regimen that we have used appeared thus to cancel some of the major prognostic factors, the only remaining significant one being the type of response. Our data collection did not allow us to study the prognostic implication of multiple or specific metastatic sites [20].

In conclusion, CAVE is an intensive induction regimen that has been shown active but rather toxic. It should be emphasized that, although it seems logical to expect that more intensive treatment would be associated with an increased survival, this has not been so far clearly demonstrated in SCLC [21]. Relatively low dosage chemotherapy regimens with little toxicity have been reported to give at least as good results as more aggressive therapies in phase II studies [22, 23]; further controlled studies

in this field would be highly helpful. On the other hand improvement of the present results could be obtained by various ways: addition of other active drugs, late reinduction [24] or alternation of irradiation with chemotherapy [25] as reported by Arrigada *et al.* who obtained a 91% complete response rate with a 20 month median survival time in patients with SCLC limited disease and treated by CAVE alternating with chest irradiation. So further investigations are necessary to determine the optimal place of this intensive induction regimen in the management of SCLC.

REFERENCES

1. Klastersky J, Nicaise C, Longeval E *et al.* Cisplatin, adriamycin and etoposide (CAV) for remission induction of small cell bronchogenic carcinoma. *Cancer* 1982, **50**, 652–658.
2. Klastersky J, Sculier JP, Dumont JP *et al.* Combination chemotherapy with adriamycin, etoposide and cyclophosphamide for small cell carcinoma of the lung. *Cancer* 1985, **56**, 71–75.
3. Aisner J, Wiernik PH. Chemotherapy versus chemo-immunotherapy for small cell undifferentiated carcinoma of the lung. *Cancer* 1980, **46**, 2543–2549.
4. Abeloff MD, Ettinger DS, Order SE *et al.* Intensive induction chemotherapy in 54 patients with small cell carcinoma of the lung. *Cancer Treat Rep* 1981, **65**, 639–646.
5. Sculier JP, Klastersky J, Nguyen Thi H *et al.* Polychimiothérapie du cancer bronchique indifférencié à petites cellules. *Presse Médicale* 1986, **15**, 835–838.
6. Sierocki JS, Hilaris BS, Hopfan S *et al.* *Cis*-dichlorodiammineplatinum (II) and VP16-213: an active induction regimen for small cell carcinoma of the lung. *Cancer Treat Rep* 1979, **63**, 1593–1597.
7. Giaccone G, Musella R, Donadio M *et al.* Chest irradiation as an attempt to improve the response after induction chemotherapy in small cell lung carcinoma. *Acta Radiol Oncol* 1985, **24**, 475–479.
8. Evans WK, Shepherd FA, Feld R *et al.* VP-16 and cisplatin as first line therapy for small cell lung cancer. *J Clin Oncol* 1985, **3**, 1471–1477.
9. Sculier JP, Klastersky J, Strijckmans P and the EORTC Lung Cancer Working Party (Belgium). Late intensification in small cell lung cancer: a phase I study of high doses of cyclophosphamide and etoposide with autologous bone marrow transplantation. *J Clin Oncol* 1985, **3**, 184–191.
10. Johnson BE, Ihde DC, Bunn PA *et al.* Patients with small cell lung cancer treated with combination chemotherapy with or without irradiation. Data on potential cures, chronic toxicities and late relapses after a five to eleven year follow up. *Ann Intern Med* 1985, **103**, 430–438.
11. Livingston RB, Stephens RL, Bonnet JD *et al.* Long-term survival and toxicity in small cell lung cancer. Southwest Oncology Group Study. *Am J Med* 1984, **77**, 415–417.
12. Vogelsang GB, Abeloff MD, Ettinger DS, Booker SV. Long-term survivors of small cell carcinoma of the lung. *Am J Med* 1985, **79**, 49–56.
13. Aisner J, Alberto P, Bitran J *et al.* Role of chemotherapy in small cell lung cancer: a consensus of the International Association for the Study of Lung Cancer Workshop. *Cancer Treat Rep* 1983, **67**, 37–43.
14. Aisner J, Whitacre M, Van Echo DA *et al.* Doxorubicin, cyclophosphamide and VP16–213 (ACE) in the treatment of small cell lung cancer. *Cancer Chemother Pharmacol* 1982, **7**, 187–193.
15. 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.
16. Cunningham D, Banham SN, Hutcheon AH *et al.* High dose cyclophosphamide and VP-16 as late dosage intensification therapy for small cell carcinoma of lung. *Cancer Chemother Pharmacol* 1985, **15**, 303–306.
17. Markman M, Abeloff MD, Berkman AW, Waterfield WC. Intensive alternating chemotherapy regimen in small cell carcinoma of the lung. *Cancer Treat Rep* 1985, **69**, 161–166.
18. Maurer LH, Pajak TE. Prognostic factors in small cell carcinoma of the lung: a Cancer and Leukemia Group B Study. *Cancer Treat Rep* 1981, **65**, 767–774.
19. Souhami RL, Bradbury I, Geddes DM *et al.* Prognostic significance of laboratory parameters measured at diagnosis in small cell carcinoma of the lung. *Cancer Res* 1985, **45**, 2878–2882.
20. Ihde DC, Makuch RW, Carney DN *et al.* Prognostic implications of stage of disease and sites of metastases in patients with small cell carcinoma of the lung treated with intensive combination chemotherapy. *Am Rev Respir Dis* 1981, **123**, 500–507.
21. Sculier JP, Klastersky J. Intensive chemotherapy in small cell lung cancer. *Eur J Cancer Clin Oncol* 1986, **22**, 1417–1420.
22. Kessinger A, Foley JF, Lemond HM. Therapeutic management of small cell lung cancer. Fewer toxic reactions with lower chemotherapeutic drug dosages. *J Am Med Assoc* 1983, **250**, 3188–3191.
23. Allan SG, Grogor A, Cornbleet MA *et al.* Phase II trial of vindesine and VP16-213 in the palliation of poor prognosis patients and elderly patients with small cell lung cancer. *Cancer Chemother Pharmacol* 1984, **13**, 106–108.
24. Livingston RB, Mira JG, Chen TT *et al.* Combined modality treatment of extensive small

cell lung cancer: a Southwest Oncology Group Study. *J Clin Oncol* 1984, **2**, 585–590.
25. Arrigada R, Le Chevalier T, Baldeyrov P *et al.* Alternating radiotherapy and chemotherapy schedules in small cell lung cancer limited disease. *Int J Radiat Oncol Biol Phys* 1985, **11**, 1461–1467.