Cancer Chemother Pharmacol (1989) 24: 381–385

Cancer Chemotherapy and Pharmacology

Combination chemotherapy with cisplatin and etoposide associated with radiotherapy in the treatment of small-cell lung cancer

F. Figoli[1*], A. Veronesi[1], M. G. Trovo'[2], D. Errante[1], M. Della Valentina[1], V. Zagonel[1], R. Talamini[3], M. D. Magri[1], and S. Monfardini[1]**

[1] Division of Medical Oncology, [2] Division of Radiotherapy, [3] Epidemiology Unit, Centro di Riferimento Oncologico, Aviano, Italy

Summary. A total of 52 consecutive, previously untreated patients with small-cell lung cancer (SCLC) were scheduled to receive six cycles of a combination of etoposide (75 mg/m^2 per day) and cisplatin (20 mg/m^2 per day), each cycle given over 5 consecutive days. In all, 28 patients had extensive disease (ED) and 24, limited disease (LD). After three cycles of chemotherapy, all responding patients were given chest radiotherapy (RT) (45 Gy in two split courses and 30 Gy in LD and ED, respectively); only patients with LD who achieved complete remission (CR) after three cycles of chemotherapy were given prophylactic brain irradiation (30 Gy). In the 51 evaluable patients, the overall response rate was 90%, with a 31% CR and a 59% partial remission (PR) rate. In LD and ED patients, 57% and 11% CR rates and 30% and 82% PR rates were noted, respectively. Myelosuppression was the most frequently observed toxicity. The median duration of response was 12 months in LD (range, 3–41+ months) and 7 months (range, 2–12 months) in ED; the median survival was 15 months in LD and 9.3 months in ED, respectively. In all 30% of LD patients are alive and well at a minimal follow-up of 18 months. This trial confirms the activity of the cisplatin-etoposide combination in SCLC.

Introduction

The most substantial progress in the treatment of small-cell lung cancer (SCLC) has been obtained using combinations of cytotoxic drugs. In previously untreated patients with SCLC, etoposide is one of the most active agents, with response rates ranging from 20% to 60% [1, 5]. Although the efficacy of cisplatin in previously treated patients is marginal [7, 12], its addition to etoposide in experimental models produces a synergistic action [18]. The combination of cisplatin and etoposide (PE) has been reported to be active as second-line treatment even in patients previously treated with etoposide [10, 16]. Trials reporting data on front-line therapy with PE show that this regimen produces a high response rate, usually obtained within the 1st weeks of treatment [9, 21].

Analysis of the pattern of relapse indicates that the chest is the most frequent site of recurrence. Radiotherapy (RT), even when given at high doses, does not affect survival; however, its omission leads to an increase in the incidence of initial relapse at the primary tumor site in both limited (LD) and extensive (ED) SCLC [6, 8, 13, 15]. This paper reports the results of a prospective study aiming to define further the role of the PE regimen as front-line treatment associated with RT in patients with SCLC.

Materials and methods

From February 1984 until September 1986, all consecutive, eligible patients seen at our institution were enrolled into the study. Conditions of eligibility included: histological or cytological proof of SCLC, age of <75 years, Karnofsky performance status (PS) of >40, serum creatinine values within normal limits, and no previous treatment. Staging procedures included clinical examination, chest X-rays, bronchoscopy, isotopic bone and liver scans, bone marrow aspirate and biopsy, peripheral blood cell count, determination of plasma urea, electrolytes, and serum creatinine, and serum liver function tests. Disease stage was classified as limited disease (LD), defined as tumor involvement confined to one hemithorax, including ipsilateral supraclavicular nodes, or extensive disease (ED), with tumor beyond these sites; patients with malignant pleural effusion were considered to have ED.

Patients received three cycles of induction chemotherapy comprising 75 mg/m^2 etoposide given as a 45-min i.v. infusion for 5 consecutive days and 20 mg/m^2 cisplatin given i.v. on the same days. Courses were repeated every 3 weeks. Prior to cisplatin, 500 ml i.v. fluids with 100 g mannitol were given. No further routine hydration was given if patients could maintain adequate (2 l/day) oral fluid intake; otherwise, an additional 1,000–1,500 ml i.v. fluids were given. Peripheral blood cell counts, renal function tests, and chest X-rays were carried out before each course of treatment; after three cycles, bronchoscopy and all initially positive examinations were repeated.

At that point, responding patients with LD received chest RT (25 Gy in ten sessions), followed by a fourth cycle of PE at the same dose as that given for induction. After a 3-week rest, responders were given 20 Gy in ten further sessions; patients achieving complete remission (CR) after three cycles of induction chemotherapy underwent prophylactic cerebral irradiation (PCI), receiving

* *Present address:* Oncology Department, General Hospital "S. Bortolo", Vicenza, Italy
** Bursar, Italian Association for Cancer Research (AIRC)
Offprint requests to: Andrea Veronesi, Division of Medical Oncology, Centro di Riferimento Oncologico, I-33081 Aviano, Italy

30 Gy in ten sessions. With the etoposide dose reduced to 50 mg/m^2, another two cycles of PE were given after the RT course to complete the treatment of LD patients. After three induction PE cycles, responding patients with ED received a single cycle of chest RT (30 Gy in ten sessions) without PCI, followed by three cycles of PE, in which the etoposide dose was again reduced to 50 mg/m^2. Therefore, a total of six PE cycles were given to both LD and ED patients Figure 1).

At the end of treatment, responses were reassessed by repeat examination of all disease parameters. No further treatment was given to patients in clinical CR at the end of treatment, even if microscopic residual disease was noted (failure to obtain pathological CR). Patients resistant to chemotherapy or relapsing within 6 months from the end of treatment received, 600 mg/m^2 i.v. cyclophosphamide, 40 mg/m^2 i.v. Adriamycin, and 40 mg/m^2 i.v. methotrexate every 3 weeks as salvage chemotherapy (CAM regimen).

Tumor response and toxicity were defined according to standard WHO criteria [14]; actuarial survival and response duration were calculated according to the life-table method [2]. A total of 52 eligible patients were enrolled in the study from February 1984 until September 1986. Their main characteristics are reported in Table 1.

Results

One patient was not evaluable because he refused treatment. Of the 51 evaluable patients, 46 responded to the overall treatment with 16 (31%) CRs and 30 (59%) partial remissions (PRs), for an overall response rate of 90%; 3 (6%) showed a minor response, and 2 died within 1 month from the start of therapy due to progressive disease and myocardial infarction, respectively. At evaluation after three cycles, the same 90% response rate was noted. Only one PR was converted into a CR after RT and three additional chemotherapy cycles.

Of the 23 LD patients, 20 (87%) responded: 13 (57%) achieved a clinical CR (pathologically confirmed in 12) and 7 (30%), a PR. In the 28 ED patients, 3 (11%) CRs were encountered. ED patients achieving a CR had extensive SCLC due to contralateral supraclavicular nodes. An additional 23 (82%) ED patients achieved a PR. The overall response rate in ED patients was therefore 93%. All three patients presenting with superior vena cava obstruction showed immediate relief of their symptoms after the beginning of chemotherapy.

Responses lasted for a median of 12 months (range, 3–41+ months) in LD and 7 months (range, 2–12 months) in ED. The actuarial median duration of response was 14 and 8 months for CR and PR, respectively. Sites of relapse are shown in Table 2. As the initial sign of progression, chest relapse occurred in only 11 patients (5%); most patients underwent relapses in distant sites. The high incidence of brain metastasis is noteworthy; only 3/22 patients relapsing in the brain had received PCI.

Second-line chemotherapy with CAM was given to eight patients; no objective response was noted in the six evaluable patients.

All patients but one were evaluable for toxicity; the unevaluable patient refused treatment and was lost to follow-up. Myelosuppression was the main toxicity (Table 3), occurring in 48 of 51 patients (94%); 23% had grade III–IV myelotoxicity, with 1 patient dying due to granulocytopenia with infection. Another patient experienced mild, reversible infection, and one more died within 1 month of the start of induction treatment; the cause of death is unknown. Anemia occurred in 70% of patients and 18 (35%) required blood transfusions. Thrombocytopenia was noted in 50% of patients, although none experienced bleeding. In all, 36 (70%) patients required at least one treatment delay due to myelosuppression.

Nausea and vomiting were almost universal. Transient elevation in serum creatinine was noted in 22 patients who needed forced diuresis without treatment discontinuation; however, 4 of these patients had a treatment delay. In three additional patients, renal toxicity was more severe; chemotherapy was continued with etoposide alone in one

Table 1. Patient characteristics

Total number	52
Median age	62 years (range, 47–73 years)
Sex ratio (M/F)	44/8
Performance status:	
80–100	34
50–70	18
Stage:	
Limited	24
Extensive	28
Sites of metastatic disease:	
Lymph nodes	9
Bones	17
Pleura	7
Pericardium	2
Liver	6

Table 2. Sites of initial relapse (44 patients)

Ipsilateral lung	2
Contralateral lung	5
Pleura	2
Bones	8
Liver	5
Brain	22
Small bowel	1
Pancreas	1
Supraclavicular lymph nodes	4

Table 3. Toxicity (51 evaluable patients)

	WHO grade				
	0	1	2	3	4
Leukopenia	3 (6)	16 (31)	20 (39)	8 (16)	4 (8)
Thrombocytopenia	25 (49)	16 (31)	5 (10)	5 (10)	0
Anemia	24 (47)	10 (20)	15 (29)	2 (4)	0
Nausea and vomiting	3 (6)	10 (20)	17 (33)	21 (41)	0
Renal	26 (51)	22 (43)	2 (4)	1 (2)	0
Infection	49 (96)	0	1 (2)	1 (2)	0
Neurotoxicity	43 (84)	7 (14)	1 (2)	0	0

Numbers in parentheses indicate percentage of patients

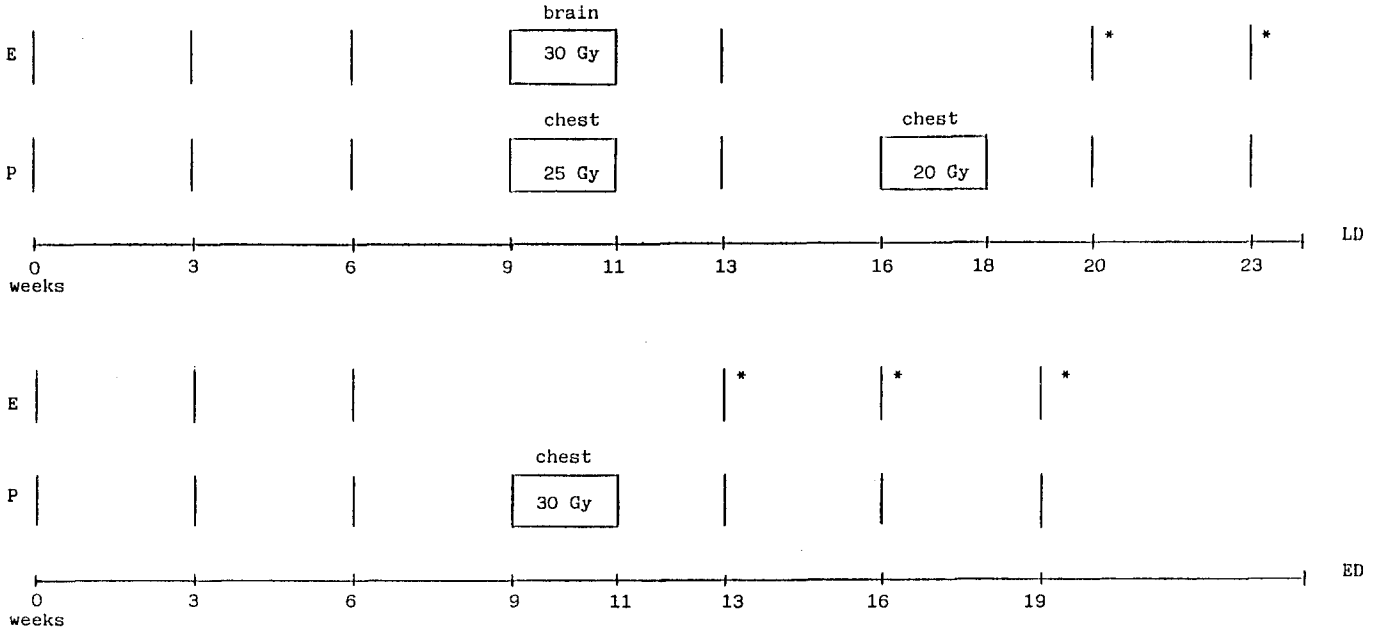

Fig. 1. Treatment schedule outline. *LD*, limited disease; *ED*, extensive disease; *P*, cisplatin; *E*, etoposide; *, attenuated dose

patient after three courses and was stopped in the other two after three and four cycles, respectively.

Almost all patients received chemotherapy on an outpatient basis; only 19 (36%) required hospitalization during the first cycles, either because they were very symptomatic (9 patients) or due to complications of treatment or the need for supportive therapy (10 patients). A total of 16 patients (31%) did not complete the planned treatment because of refusal after three PE courses and RT (8 patients), nephrotoxicity (3), or hematological toxicity (5).

Median survival (MS) in the whole patient group was 10.3 months. Patients with LD survived significantly longer than those with ED (15 vs 9.3 months; $P < 0.001$). Seven LD patients are still alive and well at a minimal follow-up of 18 months, representing 30% of LD patients; five of the long-term survivors achieved a pathological CR after three cycles of PE. The initial performance status (PS) did not significantly affect survival, with MS of 10.8 and 9.7 months in patients with a PS of 80–100 and 40–70, respectively ($P = 0.1$).

Discussion

The results of the present study confirm the high response rate obtained in previous trials with PE as front-line treatment. As pointed out by other authors [9, 21], PE produces an objective response in the majority of patients within a few weeks. We obtained an overall response rate of 90%, with a 31% CR rate; all responsive patients obtained at least a PR after two cycles of treatment. Moreover, the survival of the 16 patients not completing treatment because of either refusal or toxicity is superimposable on overall survival. These findings suggest that even shorter treatments might be considered, as has been indicated by other authors [22, 24]. Three patients presenting with superior vena cava obstruction received PE as first-line treatment, showing complete resolution of their symptoms after one course of therapy. MS was 15 and 9 months in LD and ED patients, respectively.

Table 4 shows the results obtained by several groups with the PE combination and with the combination of carboplatin (a cisplatin derivative with a different spectrum of toxicity) and etoposide [3, 4, 9, 11, 17, 19, 21, 23]. Response and MS in our series of patients were in the range obtained by other authors with either PE or carboplatin-etoposide. All studies report a high response rate in excess of 80%. Boni et al. [4] obtained an MS of 60 weeks in LD and 41 weeks in ED and Scher et al. [19], an MS of 18 and 8 months in LD and ED, respectively, whereas in a poor-risk group of patients, Evans et al. [9] reported a 70-week survival in LD and a 43-week survival in ED.

In the present study, the addition of chest RT led to a low (24%) rate of chest relapse, with a local failure incidence that compares favorably with that obtained in trials without RT [13, 15]. Unfortunately, satisfying control of local relapse in this study did not influence survival, which was similar to that reported in trials in which RT was not mandatory, confirming that systemic spread represents the major problem whose better control is critical to the treatment of SCLC.

The most frequent side effects were myelosuppression and gastrointestinal toxicity, as in previous trials using front-line treatment with PE [4, 9, 11, 17, 19, 21]. The grade III–IV leukopenia noted in 23% of our patients, as well as the incidence of anemia and thrombocytopenia, were similar to Evans' data [9]. In the present study, a transient increase in serum creatinine occured in 50% of patients, with 7%–8% requiring treatment discontinuation. These figures are superimposable on those reported by Evans.

In our previous experience with the PE regimen in relapsed patients with SCLC [10] and in non-SCLC [25, 26], only 11% and 20% of patients, respectively, showed a mild elevation of serum creatinine levels. The total number of cycles given is probably an important factor in explaining

Table 4. Results obtained with front-line therapy comprising etoposide plus cisplatin and etoposide plus carboplatin

Authors	Number of patients (LD/ED)	Treatment (mg/m^2)	Response rate (%)	CR rate (%)	Median survival
Sieroki et al. [21]	21/17[a]	P60, day 1; E120, days 4, 6, 8	94	47	LD 14 months ED 9 months
Kim + McDonald [11]	11/13	P75, day 1; E125, days 1, 3, 5	87	25	NR
Evans et al. [9]	11/17	P25, days 1–3; E100, days 1–3	85	42	LD 70 weeks ED 43 weeks
Salvati et al. [17]	18/0[a]	P60, day 1; E120, days 2, 3, 4	89	39	52 weeks
Boni et al. [4]	12/10	P60, day 1; E120, days 4, 6, 8	95	59	LD 60 weeks ED 41 weeks
Scher et al. [19]	37	P125, day 1; E120, days 4, 6, 8	84	54	LD 18 months ED 8 months
Smith et al. [23]	28/24	C300, day 1; E100, days 1–3	85	21	9, 5 months
Bishop et al. [3]	36/58	C100, days 1–3; E120, days 1–3	77	40	LD 15, 3 months ED 8, 3 months
Present report	24/28	P20, days 1–5; E75, days 1–5	90	31	LD 15 months ED 9.3 months

[a] PE treatment followed by other regimens
P, cisplatin; E, etoposide; C, carboplatin; NR, not reported

these differences. Patients resistant to or relapsing after PE treatment in our trial did not respond to salvage treatment with CAM; although the number of such patients is small, our data confirm observations by others [20] indicating that non-platinum-containing combinations are ineffective in patients resistant to PE.

In conclusion, PE appears to be a reasonable standard regimen in SCLC, with reproducible activity not inferior to that of carboplatin-containing schemes. Its eventual superiority over other regimens can be ascertained only by randomized studies.

References

1. Arnold AM (1979) General review. Podophyllotoxin derivative VP 16–213. Cancer Chemother Pharmacol 3: 71–80
2. Benedetti J, Yean K, Young L (1983) BMDP statistical software. University of California Press, Berkeley, pp 557–575
3. Bishop JF, Raghavan D, Stuart-Morris R, Morstyn G, Aroney R, Kefford R, Yven K, Lee J, Gianoutsos P, Olver N, Zalcberg J, Ball D, Bull C, Fox R (1987) Carboplatin (CBCDA, JM8) and VP16-213 in previously untreated patients with small cell lung cancer. J Clin Oncol 5: 1574–1578
4. Boni C, Bisagni G, Ceci G, Cuomo A, Consigli GF, Peracchia G, Cocconi G (1985) Cis-platinum plus VP16 chemotherapy as a front line treatment in small cell lung cancer. Proc Am Soc Clin Oncol 4: 196
5. Cavalli F, Sonntag RW, Jung F, Senn HJ, Brunner KW (1978) VP16-213 monotherapy for remission induction of small cell lung cancer. A randomized trial using three dosage schedules. Cancer Treat Rep 62: 473–475
6. Chak LY, Daniels JR, Sikich BI, Torti FM, Lockbaum P, Carter SK (1982) Patterns of failure in small cell carcinoma of the lung. Cancer 50: 1857–1863
7. Dombernowsky P, Sorensen S, Aisher J (1979) *cis*-Dichlorodiammineplatinum in small cell anaplastic bronchogenic carcinoma: a phase II study. Cancer Treat Rep 63: 543–545
8. Elliot JA, Osterlind K, Hirsch FR, Hansen HH (1984) Metastatic patterns in small-cell lung cancer: correlation of autopsy findings with clinical parameters in 537 patients. J Clin Oncol 2: 585–590
9. Evans WK, Sheperd FA, Feld R, Osoba D, Dang P, Deboer G (1985) VP16 and cisplatin as first-line therapy for small cell lung cancer. J Clin Oncol 3: 1471–1477
10. Figoli F, Veronesi A, Ardizzoni A, Canobbio L, Bruschi G, Mazza F, Lo Re G, Zagonel V, Rosso R, Monfardini S (1988) Cisplatin and etoposide as second line chemotherapy in patients with small cell lung cancer. Cancer Invest 6(1): 1–5
11. Kim PN, McDonald DB (1982) The combination of VP16-213 and cis-platinum in the treatment of small cell carcinoma of the lung. Proc Am Soc Clin Oncol 1: 141
12. Levenson MR, Ihde CD, Hubermen MS, Cohen MH, Bunn AP, Minna JD (1981) Phase II trial of cisplatin in small cell lung carcinoma of the lung. Cancer Treat Rep 65: 905–907
13. Livingston RB, Mira JG, Chen T, McGraven M, Costanzi JJ, Samson M (1984) Combined modality treatment of extensive small cell lung cancer. A Southwest Oncology Group study. J Clin Oncol 6: 585–590
14. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47: 207–214
15. Mira JG, Livingston RB, Moore TN, Chen T, Batley F, Bogardus CR, Considine B, Mansfield CM, Schlosser J, Seydel G (1982) Influence of chest radiotherapy in frequency and patterns of chest relapse in disseminated small cell lung cancer. A Southwest Oncology Group study. Cancer 50: 1266–1272
16. Porter LL, Johnson DM, Hainsworth JD, Hende KR, Greco A (1985) Cisplatin and etoposide combination chemotherapy for refractory small cell carcinoma of the lung. Cancer Treat Rep 69: 479
17. Salvati F, Mugnaini L, Cruciani AR (1985) Cisplatin and etoposide followed by Adriamycin and Cytoxan for treatment of SCLC limited disease. Proceedings of the IVth World Conference on Lung Cancer, Toronto, abstract 523
18. Schabel FM, Trader MW, Laster WR, Corbett TH Griswold DP (1979) *cis*-Dichlorodiammineplatinum(II) combination chemotherapy and cross-resistance studies with tumors of mice. Cancer Treat Rep 63: 1459–1473
19. Scher H, Casper E, Gralla R, Shank B, Kelsen D, Bosl G, Kris M, Hollander P, Martini N, Wittes R (1985) Intensive induction chemotherapy with cisplatinum + etoposide with radiotherapy for small cell lung cancer. Proceedings of the IVth World Conference on Lung Cancer, Toronto, abstract 483

20. Sculier JP, Klastersky J, Libert P, Rovez P, Thiriaux J, Michel J, Bureau G, Brohee D, Mommen P (1987) Cyclophosphamide, Adriamycin and vincristine (CAVi): an ineffective second-line chemotherapy regimen for small cell lung cancer. Proc Am Soc Clin Oncol 6: 184
21. Sierocki JS, Hilaris BS, Hopfan S, Martini N, Berton D, Golbey RB, Wittes RE (1979) *cis*-Dichlorodiammineplatinum(II) and VP16-213: an active induction regimen for small cell carcinoma of the lung. Cancer Treat Rep 63: 1593–1597
22. Smith IE, Sappino AP, Bandy PR (1981) Long-term survival five years or more after combination chemotherapy and radiotherapy for small cell lung carcinoma. Eur J Cancer Clin Oncol 17: 1249–1253
23. Smith IE, Evans BD, Gore ME, Vincent DM, Repetto L, Yarnold YR, Ford HT (1987) Carboplatin (Paraplatin; JM 8) and etoposide (VP16) as first-line combination therapy for small cell lung cancer. J Clin Oncol 5: 185–189
24. Thatcher N, James RD, Steward WP, Barber PV, Feinmann BA, Lawson A, Carroll KB (1985) Three months' treatment with cyclophosphamide, VP16-213 followed by methotrexate and thoracic radiotherapy for small cell lung cancer. Cancer 53: 1332–1336
25. Veronesi A, Zagonel V, Santarossa M, Tirelli U, Galligioni E, Trovo' MG, Tumolo S, Grigoletto E (1983) Cis-platinum and etoposide combination chemotherapy of advanced non-oat cell bronchogenic carcinoma. Cancer Chemother Pharmacol 11: 35–37
26. Veronesi A, Magri MD, Tirelli U, Carbone A, Mazza F, Franceschi S, Talamini R, Ardizzoni A, Canobbio L, Rosso R, Monfardini S (1988) Chemotherapy of advanced non-small cell lung cancer with cyclophosphamide, Adriamycin, methotrexate, and procarbazine versus cisplatin and etoposide: a randomized study. Am J Clin Oncol (CCT) 11: 566–571

Received 10 November 1988/Accepted 10 March 1989