A Randomized, Controlled Phase III Study of Cyclophosphamide, Doxorubicin, and Vincristine with Etoposide (CAV-E) or Teniposide (CAV-T), Followed by Recombinant Interferon-α Maintenance Therapy or Observation, in Small Cell Lung Carcinoma Patients with Complete Responses

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BACKGROUND. Studies of chemotherapy for patients with small cell lung carcinoma (SCLC) have shown that teniposide (T) may have higher activity than etoposide (E). In this randomized, controlled Phase III study, the authors compared cyclophosphamide, doxorubicin, and vincristine (CAV) with E and CAV with T as induction treatments for patients with SCLC. A second objective of the study was to study patients who had achieved complete response (CR). They were considered for a second randomization to maintenance therapy, in which they would receive either recombinant interferon-α (rIFN-α) or no treatment.

METHODS. From June 1990 to December 1995, 140 untreated SCLC patients were enrolled in this study. Patients were stratified by either limited disease (LD) or extensive disease (ED) and randomized to one of two treatment arms. The schedules for both arms included cyclophosphamide 1000 mg/m^2 administered intravenously (i.v.), doxorubicin 50 mg/m^2 i.v., and vincristine 2 mg i.v. on Day 1. Arm A (CAV-E) involved the addition of E 100 mg/m^2 i.v. on Days 2, 3, and 4; Arm B (CAV-T) involved the addition of T 60 mg/m^2 i.v. on Days 2, 3, and 4. Courses were repeated every 3 weeks. After 3 courses, patients with LD received chest radiotherapy and 2 additional consolidation courses, whereas patients with ED received 5 consecutive courses only. Patients with CR were considered for the second randomization, which consisted of either maintenance therapy with intramuscular (i.m.) rIFN-α-2b, 3 M.U., once a day for 9 months (IFN-α arm) or no therapy (control arm).

RESULTS. At 5 years from start-up (3-year median observation time and 90% death rate), the study was closed. Results were as follows: 140 patients (71 in Arm A and 69 in Arm B) were eligible for survival analysis; 131 were evaluable for response and toxicity (66 in Arm A and 65 in Arm B), whereas 9 were not (6 early deaths and 3 with protocol violations). Among evaluable patients, 68 showed LD (35 assigned to Arm A and 33 to Arm B); the responses to treatment were 28.5% (10/35) CR and 51% (18/35) partial response (PR) to CAV-E, and 39% (13/33) CR and 39% PR (13/33) to CAV-T. Sixty-three patients showed ED (31 assigned to Arm A

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and 32 to Arm B); their responses were 22.5% (7/31) CR and 52% (16/31) PR to CAV-E, and 12.5% (4/32) CR and 50% (16/32) PR to CAV-T. Drug-related toxicity was WHO Grade 3–4 myelosuppression in 20% of 292 CAV-E courses and in 27% of 252 CAV-T courses. There were 6 toxic deaths, 1 in Arm A and 5 in Arm B (chi-square = 2.86); 2 patients in Arm A discontinued therapy due to persistent leukopenia and thrombocytopenia. No other remarkable toxicities were observed. Actuarial median survival (MS) was 13.7 months (range, 1.0–62.5 months) for patients with LD receiving CAV-E (Arm A) and 15.2 months (range, 0.5–68.2 months) for those receiving CAV-T (Arm B) (chi-square = 0.89); in patients with ED it was 10.5 months (range, 0.6–30.4 months) and 8.2 months (range, 0.2–24.8 months), respectively (chi-square = 3.42). Overall, MS was 12 months (range, 0.6–62.5 months) in Arm A and 10 months (range, 0.2–68.2 months) in Arm B (chi-square = 0.059). Thirty-nine patients with CR (27.8%) were candidates for the second randomization. Among them, 26 patients (18.5%) complied with the program and were randomized as follows: 14 were assigned to the IFN-α arm and 12 to the control arm. Starting from the second randomization, median time to progression was 12 months (range, 3–51 months) for patients in the IFN-α arm versus 7 months (range, 1–59 months) for patients in the control arm (chi-square = 0.12). MS was 15 months (range, 5–52.3 months) versus 9 months (range, 2–60.5 months) (chi-square = 0.13).

CONCLUSIONS. This study did not show a wide difference in activity and toxicity between CAV-E and CAV-T. The number of patients who entered the second randomization was too small to reach the second study endpoint. ***Cancer* 1997;80:2222–9.** © *1997 American Cancer Society.*

KEYWORDS: Phase III trial, treatment, small cell lung carcinoma, maintenance therapy, chemoimmunotherapy, podophillotoxins, interferon.

Over the last decade, chemotherapeutic treatment of small cell lung carcinoma (SCLC) has reached a plateau. Current regimens give high response rates, but median survival (MS) remains 12–14 months (mos), and long term survivors are 5–10%.[1] Generally, patients with SCLC respond to chemotherapy, but within 1–2 years from diagnosis they relapse and die of their disease. No effective strategies exist to avoid recurrence or improve survival. New drugs and innovative approaches are urgently needed. Currently, drug combinations such as CAV (cyclophosphamide, doxorubicin, and vincristine) or PL/E (cisplatin and etoposide) are considered ''standard'' treatment.[2] Podophyllotoxins derivatives such as etoposide (E) or teniposide (T) are considered very active compounds against SCLC.[3–6] E, when used in a single drug schedule, produced 30–60% response rates in chemotherapy-naive patients and in combination with CAV offered better results than CAV alone.[7–9] T also showed promising results; in in vitro studies, it demonstrated 5–10% higher cytotoxic activity than E.[10,11] T offered 25–30% response rates in pretreated patients and up to 90% response rates in untreated patients.[12–14] However, T, given in a multidrug schedule for treating SCLC, has not been extensively investigated, and further studies are warranted.

In the search for innovative strategies against SCLC, biologic agents such as natural or recombinant interferons (rIFNs) have recently been reconsidered for SCLC treatment programs.[15–19] Laboratory studies have demonstrated that rIFNs were able to enhance drug activity and restore some classes of histocompatibility antigens whose expression was decreased in SCLC cell lines.[20–22] Mattson et al.,[15] using natural IFN-α as maintenance therapy for patients with SCLC responding to induction therapy, reported an advantage in survival for a subset of patients with limited disease. In this randomised Phase III study, the results for the IFN-α arm were significantly superior to those for either the chemotherapy arm or the control arm. Conversely, Kelly et al.,[16] in a similar Southwest Oncology Group (SWOG) study, did not find a survival advantage in comparing IFN-α to observation only, and Jett et al.[17] reported negative results from comparing IFN-γ to no treatment. However, to date there are few reports on this topic, and data still remain undefined.

The current study had two main objectives. The first was to compare E with T in a multidrug schedule as induction chemotherapy for SCLC (CAV-E vs. CAV-T). The latter was to assess the role of rIFN-α as maintenance therapy for patients with complete responses (CRs).

PATIENTS AND METHODS

Patients from 8 participating institutions with chemotherapy-naive, histologically or cytologically proven SCLC were enrolled in this randomized trial. Clinical prerequisites for the study entry were age < 75 years; life expectancy longer than 2 months; Karnofsky performance status (KPS) of 60–100; Eastern Cooperative Oncology Group (ECOG) 0–2; measurable or evaluable disease; no prior chemoradiotherapy; no brain metastases; normal cardiac, liver, and renal functions; adequate bone marrow reserve; and no history of other malignancies. Before randomization, verbal informed consent was obtained according to our treatment policy. Before treatment, patients underwent the following staging procedures: physical examination, electrocardiography, blood chemistries, chest X-ray, bronchoscopy, whole body computed tomography (CT) scan, and liver ultrasonography. Bone scan and bone marrow biopsy were also performed. Further investigations were carried out when clinically indicated. The stage of disease was assessed as limited disease (LD) when confined to one hemithorax, the mediastinum, and ipsilateral hilar and supraclavicular lymph nodes; all other conditions were defined as extensive disease (ED).[23]

Treatment Program

All patients eligible for the study were stratified by LD or ED and then randomized to receive or CAV-E or CAV-T. The CAV treatment schedule consisted of cyclophosphamide 1000 mg/m^2 administered intravenously (i.v.) on Day 1, doxorubicin 50 mg/m^2 i.v. on Day 1, and vincristine 2 mg/m^2 i.v. on Day 1; this was followed by E 100 mg/m^2 i.v. on Days 2, 3, and 4 (Arm A) or by T 60 mg/m^2 i.v. on Days 2, 3, and 4 (Arm B); courses were repeated every 3 weeks. After 3 courses, patients with LD received chest radiotherapy and then two additional courses. Patients with ED received five consecutive courses of chemotherapy and palliative radiotherapy to the primary tumor if required. Patients with minor responses and those with progressive disease (PD), according to their KPS, received second-line chemotherapy with carboplatin (CBDCA) 300 mg/m^2 i.v. on Day 1 and either T 60 mg/m^2 i.v. on Days 2, 3, and 4 (if they had received CAV-E) or E 100 mg/m^2 i.v. on Days 2, 3, and 4 (if they had received CAV-T).

Prophylactic brain radiation was performed on patients with CR after first- or second-line therapy. Supportive care was given to all patients according to clinical requirements.

Toxicity was graded according to World Health Organization (WHO) criteria,[24] and drug dose modifications were made according to each patient's tolerance. Survival time was calculated from the date of randomization to a patients death or the date of last follow-up. Categories of tumor response were CR, PR, and no response (NR), the latter including patients with stable or PD.[25] The duration of objective response was computed from the first evidence of tumor regression until documented disease progression. Patients who had achieved CR after first- or second-line therapy were scheduled for a second randomization to receive rIFN-α-2b (Schering-Plough, Milan), 3 M.U., administered intramuscularly (i.m.), daily for 9 months (IFN-α arm) or no treatment (control arm). Dose modifications were planned for maintenance therapy with rIFN-α, according to the WHO toxicity criteria and patient tolerance. In the cases of WHO Grade 2 or higher toxicity during the first 2 weeks, the dose administration of rIFN-α was reduced from daily to three times per week; if toxicity persisted, rIFN-α was discontinued.

Statistical Considerations

Randomization was centralized and treatment arm assignment was given by telephone. Before randomization, stratification by stage of disease (LD/ED) was performed. Sample size calculation was based on an average median survival time (MS) of 12–14 months commonly observed in the SCLC patient population.[1] The original plan for the trial was that it would accrue about 240 patients. According to George and Desu statistics,[26] this number would have detected a difference in MS of 40% or more between the two arms (alpha 5%; 1 − beta = 0.8). The low accrual experienced at interim analysis[27] prompted us to a protocol amendment for sample size adjustment. A target accrual of about 70 patients per arm was identified, to detect a difference in MS of 50% or greater. Fifty-six months after the start-up, the study was closed after an accrual of 140 patients and a 90% mortality rate.

The maintenance therapy with rIFN-α was initially designed for the enrollment of about 80–90 patients with CR to treatment. Assuming that about 70% of CR patients relapse at 1–2 years, these numbers allowed for the possibility of a relapse rate reduction of up to 30–40%, with differences near to 80–100% success. After adjusting the study sample size considering about 40–50 patients, the differences to be explored could have been even greater. Survival curves were plotted by the Kaplan–Meier method and compared by the log rank test. Comparisons between subgroups were performed using the chi-square test and Fisher's exact test. Significance levels were planned with $P = 0.05$ for chi-square = 3.84.

TABLE 1
Characteristics of Enrolled Patients

Characteristic	CAV-E (Arm A)	CAV-T (Arm B)
No. of patients	71	69
Median age, yrs	63	64
(range)	(42–77)	(41–75)
M/F ratio	62/9	58/11
Extent of disease		
Limited	36	35
Extensive	35	34
Karnofsky performance status		
100	19	22
80–90	42	33
60–70	10	14
Treatment		
Median courses	4	3
(range)	(1–6)	(1–5)
Radiotherapy	39	37

RESULTS

Patient Distribution and Characteristics

The study started in June 1990 and patients accrual was closed in December 1995. One hundred forty patients were enrolled and eligible for survival; 71 patients were treated with CAV-E (Arm A) and 69 were treated with CAV-T (Arm B); 131 patients were fully evaluable for response and toxicity (66 patients in Arm A and 65 patients in Arm B). Nine patients were not evaluable, 6 because of early death and 3 because of protocol violation. Table 1 shows the characteristics of all eligible patients receiving CAV-E or CAV-T. All clinical features were well balanced in the two arms. In both arms, most patients were males with LD stage and good KPS.

Response and Toxicity

Table 2 summarizes the tumor responses of the 131 evaluable patients in both arms, according to the stage of disease (68 patients with LD and 63 with ED).

Patients with LD had the following response rates: in Arm A, among 35 patients, 10 achieved CR (28.5%) and 18 PR (51.4%); in Arm B, among 33 patients, 13 had CR (39.3%) and 13 PR (39.3%); the overall response rates were 80% and 78.7%, respectively. Median duration of response (MDR) was 5.8 months (range, 1–33.6 months) in Arm A and 6.8 mos (range, 1–22.8 months) in Arm B. Patients with ED had the following response rates: in Arm A, among 31 patients, 7 achieved CR (22.5%) and 16 PR (51.6%); in Arm B, among 32 patients, 4 achieved CR (12.5%) and 16 PR (50%); the overall response rates were 74.1% and 62.5%, respectively. MDR was 3.9 months (range, 1–22.8 months) in Arm A and 3.3 months (range, 1–11.3 months) in Arm B. The statistical comparison between response categories in the two arms showed no significant differences either in LD or ED patient groups.

Treatment intensity of patients was as follows: in Arm A, 90% of patients received a full dose schedule and 10% needed drug dose reduction ranging from 10% to 30% according to the doses scheduled, whereas in Arm B, 85% of patients received full doses and about 15% of them had drug dose reductions ranging from 15% to 50% by planned doses. In both arms, chest radiotherapy (50–60 Gy) to the primary tumor was delivered in all patients with LD and in 12 additional patients with ED.

Table 3 reports WHO hematologic and gastrointestinal toxicity observed in patients in the two arms. The incidence of toxicity was evaluated as the number of courses causing toxicity versus the total of courses delivered (292 courses of CAV-E and 252 of CAV-T). WHO Grade 3–4 myelosuppression was 20% in Arm A and 27% in Arm B, whereas WHO Grade 3–4 vomiting was 11% and 15%, respectively. Complications such as nephrotoxicity, neurotoxicity, fever, and fatal infections were reported individually. Three patients (1 in Arm A and 2 in Arm B) had transient renal failure. Nine patients in Arm A and 7 in Arm B showed mild

TABLE 2
Response by Stage of Disease in the Two Treatment Arms

	Limited disease[a]				Extensive disease			
		Response (%)				Response (%)		
Treatment	No. of patients	CR	PR	NR	No. of patients	CR	PR	NR
CAV-E	35	10 (28.5)	18 (51)	7 (20)	31	7 (22.5)	16 (52)	8 (26)
CAV-T	33	13 (39)	13 (39)	7 (21)	32	4 (12.5)	16 (50)	12 (37.5)

CR: complete response; PR: partial response; NR: no response; CAV-E: cyclophosphamide, doxorubicin, and vincristine with etoposide; CAV-T: CAV with teniposide.

[a] Patients received radiotherapy (50–60 Gy) to the primary tumor.

TABLE 3
Number of Episodes of Toxicity on the Total of Courses Delivered (CAV-E, 292 Courses; CAV-T, 252 Courses)

Toxicity	WHO grade	CAV-E (%) (Arm A)	CAV-T (%) (Arm B)
Hematologic	3	34 (12)	37 (15)
	4	23 (8)	31 (12)
Gastrointestinal	3	26 (9)	30 (12)
	4	7 (2)	8 (3)

CAV-E: cyclophosphamide, doxorubicin, and vincristine with etoposide; CAV-T: CAV with teniposide; WHO: World Health Organization.

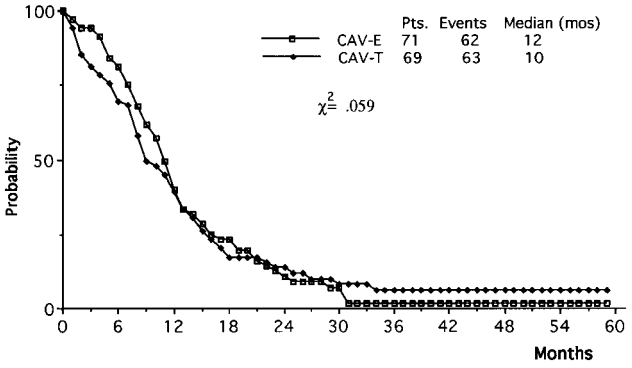

FIGURE 1. Overall survival curves for patients in both treatment arms are shown. The comparison of median survivals showed no significant difference.

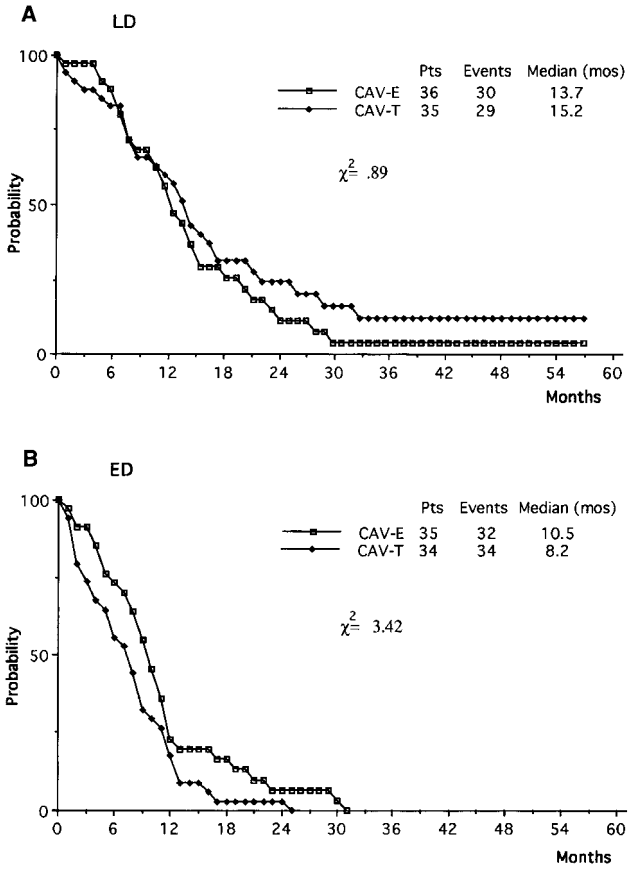

FIGURE 2. Survival curves are shown for patients with limited disease (LD) (A) and extensive disease (ED) (B). In both stage groups, a comparison of median survival by treatment showed no significant difference.

neurotoxicity consisting of peripheral paresthesias. Twenty-seven patients (10 in Arm A and 17 in Arm B) had transient fever. Due to myelotoxicity, eight patients had severe sepsis: two of them recovered with antibiotics but subsequently dismissed chemotherapy, whereas 6 became worse and died (1 treated with CAV-E and 5 treated with CAV-T; chi-square = 2.86, not significant). If clinical conditions allowed, patients in both arms who after induction therapy showed a minor response or relapse of disease, received second-line treatment with carboplatin (CBDCA) combined to E, or T, given in a crossover fashion with respect to first-line therapy (T if induction therapy had been CAV-E, and E if induction therapy had been CAV-T). Forty-three patients (22 from Arm A and 21 from Arm B) were treated with salvage chemotherapy. Patients who received CBDCA plus T achieved 3 CR and 2 PR; patients who received CBDCA plus E achieved 2 CR and 2 PR. These responsive patients were few and well balanced in the two arms, and salvage therapy as a variable was considered to have little effect on the final survival analysis.

Survival

Figure 1 shows actuarial overall survival curves for patients who received either CAV-E (Arm-A) or CAV-T (Arm-B). In both groups, MS was comparable: 12 months (range, 0.6–62.5 months) in Arm A and 10 months (range, 0.2–68.2 months) in Arm B (chi-square = 0.059). Figures 2 A and 2B show MS for patients in both arms according to stage of disease (LD and ED, respectively). In patients with LD, MS was 13.7 months (range, 1.0–62.5 months) in Arm A and 15.2 months (range, 0.5–68.2 months) in Arm B (chi-square = 0.89). In patients with ED, MS was 10.5 months (range, 0.6–30.4 months) in Arm A and 8.2 months (range, 0.2–24.8 months) in Arm B (chi-square = 3.42). The statistical comparisons among curves did not show any significant difference. At 36 months from the beginning of the study the fraction of patients still alive was 1/71 (1.4%) in Arm A and 3/69 (4.3%) in Arm B.

Maintenance Treatment (IFN-α vs. Control)

Among 140 enrolled patients in both arms, 39 achieved CR and were considered potential candidates for the

TABLE 4
Phase II–III Studies in SCLC of Interferons as Maintenance Therapy in Patients Responsive to Induction Chemoradiotherapy

Study	Stage of disease	Maintenance therapy	No. of patients/ responses	% WHO toxicity grade (3–5) H-nH	Median time to progression (mos)	Median survival (mos)	% 2-year survival	
Phase III								
Matson et al.[15]	LD & ED	IFN-α	91/R	/(1d)	/	11	18	$P < 0.01$
		vs.						
		chemotherapy	59/R	/(1d)	/	11	7	
		vs.						
		control	87/R	/(1d)	/	10	6	
Kelly et al.[16]	LD	IFN-α	64/R	15–30 (3d)	9	13	35	
		vs.						ns
		control	68/R	0	10	16	35	
Kone-Wompner et al.[29]	LD	IFN-α						
		vs.	25/R	/	13.5	16.5	/	
		control						
Jett et al.[17]	LD & ED	IFN-γ	51/CR	<50–7	6.9	13.3	27	
		vs.						ns
		control	49/CR	0	8.1	18.8	33	
Van Zandwijket et al.[30]	LD & ED	IFN-γ	59/CR	/–12 (3d)	/	8.9	/	
		vs.						ns
		control	61/CR	0	/	9.9	/	
Current study	LD & ED	IFN-α	14/CR	0–50	12	15	28	
		vs.						ns
		control	12/CR	0	7	9	25	
Phase II								
Bitran et al.[19]	ED	IFN-γ	41/R	/–/(7d)	/	/	/	
Glisson et al.[18]	ED	IFN-α	14/R	14–32	/	10	/	

LD: limited disease; ED: extensive disease; IFN: interferon; R: responders; CR: complete responders; H: hematologic; nH: nonhematologic; mos: months; (d): dead; /: not reported; ns: not significant.

second randomization. Thirty-four of those patients were coming from first-line therapy and 5 from second-line therapy. However, 13 of 39 refused further treatment, whereas 26 accepted and were randomly assigned as follows: 14 patients to the IFN-α arm and 12 patients to the control arm. Starting from the first day of second randomization, median time to progression was 12 months (range, 3–51 months) for patients treated with rIFN-α versus 7.0 months (range, 1–59 months) for patients receiving no therapy (chi-square = 0.12). MS was 15 months (range, 5–52.3 months) and 9 months (range, 2–60.5 months) in the IFN-α arm and the control arm, respectively (chi-square = 0.13).

Of the 14 patients in the IFN-α arm, none were able to comply with the planned schedule of 9 months (39 weeks) of treatment. Median treatment time for patients with rIFN-α was 12 weeks, ranging from 5 to 21 weeks. The main reasons given by most patients for the shortening of maintenance treatment with rIFN-α were side effects, such as fatigue and anorexia (65%), ''flu-like'' syndrome (50%), and fever (45%). Furthermore, to minimize secondary toxicity, 6 of the 14 treated patients received reduced rIFN-α doses after the first 3 weeks, from daily administration to three days a week. On the whole, with periodic attendance, patients seemed to accept chronic therapy unwillingly with rIFN-α, and adverse effects as noted above were not well tolerated.

DISCUSSION

Recently, drug combinations for the treatment of SCLC have been constantly subjected to changes and modulations in efforts to improve their therapeutic activity. In the current study, we attempted to enhance the activity of CAV by including T (CAV-T), and this regimen was compared with the CAV-E regimen. In the literature, when E was coupled with CAV combination, results were in some instances better than those of CAV alone. Jackson et al.,[9] using CAV-E to treat advanced SCLC patients, reported a CR of 29%, which was significantly higher than the rate of 12% observed with CAV alone. Again, Jett et al.[8] in patients with intrathoracic disease, found a significant advantage in long term survival with CAV-E compared with CAV alone (11% vs. 2%).

There is currently little experience of T alone or in a multidrug schedule for SCLC treatment. Bork et

al.[13] carried out a study with 46 patients receiving E compared with 48 patients receiving T. They reported comparable response rates with the two agents, but there was a better survival trend with T (8.5 vs. 11.3 months; *P* value not significant).

To our knowledge, in the literature there is no other trial comparing CAV-E with CAV-T.[27] In this study we attempted to compare the two schedules; and though there were some limitations due to patient sample size, our results demonstrated no superiority of CAV-T over CAV-E, and the activity of both schedules appeared substantially similar. In our comparison of the two arms, the overall response rates were equivalent, but it is noteworthy that CAV-E seemed as active in patients with ED as in those with LD. When we analyzed results in terms of MS duration and long term survival (36 months or longer), they were comparable between the two arms. Regarding toxicity, CAV-E appeared to have the advantage of a better myelotoxic profile. Fever, infections, and especially toxic deaths were less frequent in the CAV-E arm than in the CAV-T arm. Accordingly, Cherney et al.,[28] using T singularly, found unexpectedly high toxicity among SCLC patients, but this population mainly consisted of patients of advanced age.

Therefore, although higher efficacy has been reported in laboratory studies with T[10,11], our CAV-T scheme did not offer further advantages, and E remains the podophyllotoxin of choice for multimodality treatment. The second objective of our study, to evaluate rIFN-α in CR patients, failed for various reasons, the main one being the scant recruitment of patients from participating institutions. A second reason likely depended on the established criteria of patient enrollment for the second randomization; the accrual limited to CR patients seemed too restrictive. Finally, patients seldom accepted the chronic treatment that caused the well-known rIFN-α side effects. It should be noted that the authors of other studies experienced similar problems with patient compliance.

In Table 4, we have summarized data of IFN trials in SCLC; the studies are heterogeneous and results are undefined in most cases. Excluding the study by Mattson et al.,[15] whose results were significantly in favour of IFN-α therapy, the remaining were inconclusive or negative. On the whole, these studies dealt with small sample series, and patient groups are often unmatched by stage of disease, category of response (CR only, or CR plus PR), or the type of IFN used (IFN-α or IFN-γ). These differences make the interpretation of results very difficult, and to date no firm conclusion can be drawn. It is likely that a meta-analysis on available data would supply more information and shed light on this issue.

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