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Phase I/II trial of gemcitabine plus cisplatin and etoposide in patients with small-cell lung cancer

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Abstract

Objective: The objectives of this phase I/II study were to define the maximum tolerated dose (MTD), safety, and activity of cisplatin, etoposide, and gemcitabine (PEG) in the treatment of previously untreated patients with small-cell lung cancer (SCLC). *Patients and Methods:* Chemonaive patients received fixed doses of gemcitabine (1000 mg/m^2 on days 1 and 8) and cisplatin (70 mg/m^2 on day 2) and escalating doses of etoposide (starting dose of 50 mg/m^2 on days 3, 4, and 5) every 3 weeks. No prophylactic granulocyte colony-stimulating factors were used. *Results:* From September 1998 to April 2000, 56 patients with limited- or extensive-stage SCLC were enrolled and received a total of 235 cycles. Two different etoposide doses were tested in eight patients. At the second level (75 mg/m^2), two out of two patients experienced dose-limiting toxicities (neutropenia and thrombocytopenia) and no further dose-escalation was attempted, thus an etoposide dose of 50 mg/m^2 was defined as the MTD. In the subsequent phase II evaluation, 48 additional patients were enrolled, for a total of 54 patients treated at the MTD. Grade 3/4 neutropenia and thrombocytopenia occurred in 66.7 and 53.7% of patients, respectively. Non-hematologic toxicity was mild, with grade 3 diarrhea and fatigue as the main side effects. Two patients died of neutropenic sepsis (one at 75 mg/m^2 and the other at 50 mg/m^2 etoposide). Ten complete and 29 partial responses were reported, for an overall response rate of 72.2% (95% confidence interval, 56.6–85.0%). The median duration of response and median survival were 8.0 and 10 months, respectively, with a 1-year survival probability of 37.5%. *Conclusions:* The combination of PEG is feasible and well tolerated as front-line chemotherapy in SCLC. A randomized comparison of this triplet is underway.

Keywords: Cisplatin; Etoposide; Gemcitabine; Phase I/II trial; Small-cell lung cancer; Limited-stage disease; Extensive-stage disease

1. Introduction

Small-cell lung cancer (SCLC) accounts for 20–25% of all lung cancers worldwide and approximately two-thirds of patients have extensive disease at diagnosis. SCLC has been considered an extremely chemosensitive disease, and combination chemotherapy represents the cornerstone of treatment, increasing the survival of patients with limited- or extensive-stage disease. Currently, the combination of a platinum analog, cisplatin or carboplatin, with etoposide is considered a standard front-line regimen, producing overall response rates (ORR) of 60–90%, complete response (CR) of 10–15%, and median survival times of 15–20 and 7–10

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months in patients with limited- and extensive-stage disease, respectively [1,2]. Despite these results, remissions are usually temporary, due to the rapid development of resistance to chemotherapy. Therefore, cure remains an elusive goal for the majority of patients.

One possible mean to increase response and survival could derive from the intensification of front-line chemotherapy through incorporation of new drugs that demonstrated in phase II studies activity beyond 25% [3].

Gemcitabine is an antimetabolite, a new deoxycytidine analog with structural and metabolic similarities with arabinosyl cytosine [4], which, in several phase II studies, demonstrated a large spectrum of antineoplastic activity against ovarian, pancreas, bladder, and non-small-cell lung cancer (NSCLC). Cormier and coworkers used gemcitabine 1000–1250 mg/m^2 administered weekly for 3 out of 4 weeks, to treat 29 previously untreated patients with SCLC. A response rate of 27% was observed among evaluable patients and a median survival of 12 months was observed. Toxicities were mild, with only 18% of courses leading to grade 3/4 neutropenia [5]. Therefore, the good activity and the safety profile of gemcitabine suggest it is an optimal candidate for combination regimens.

Moreover, on the basis of preclinical and clinical evidence, the integration of gemcitabine with the combination of cisplatin and etoposide seemed particularly promising. First, the association between gemcitabine and cisplatin has been extensively studied in NSCLC and preclinical models revealed a multifactorial synergism between the agents, both in vitro and in vivo [6]. In several phase III studies exploring the combination of gemcitabine and cisplatin in NSCLC, response has ranged from 31 to 40.6% with neutropenia and thrombocytopenia of short duration as the main toxicities [7]. Second, gemcitabine and etoposide demonstrated schedule-dependent synergism, with a mechanism of interaction different from that of gemcitabine and cisplatin [8]. This combination was tested in a phase I study, in which SCLC patients received a fixed dose of gemcitabine 1000 mg/m^2 on days 1, 8, and 15 plus etoposide (dose escalated from 20 to 80 mg/m^2) on days 8, 9, and 10. The maximum tolerated dose (MTD) of etoposide was 80 mg/m^2; the dose-limiting toxicities (DLTs) were thrombocytopenia and neutropenia [9].

Given this promising evidence, we have undertaken this phase I/II study to determine the MTD of etoposide combined with a fixed dose of cisplatin on day 2 and fixed doses of gemcitabine on days 1 and 8, every 3 weeks, in patients with SCLC. We further defined the toxicity and activity of this novel regimen in a subsequent phase II evaluation.

2. Patients and methods

2.1. Patient selection

Eligibility criteria included histologically or cytologically proven and measurable SCLC, limited- or extensive-stage disease, age 18–75 years, World Health Organization (WHO) performance status ≤ 2, no prior chemotherapy, and no previously irradiated disease except for emergency radiotherapy. Limited-stage disease was defined as disease confined to one hemithorax, and included patients with involvement of mediastinal, hilar, or supraclavicular lymph nodes (ipsilateral or bilateral). Patients with ispilateral pleural effusion were also considered to have limited stage disease. Patients not satisfying these criteria were considered to have extensive-stage disease. In addition, patients were required to have adequate hemopoietic function (absolute neutrophil count [ANC] $\geq 1.5 \times 10^9$/l, hemoglobin ≥ 10 g/dl, and platelet count $\geq 100 \times 10^9$/l), liver function (bilirubin level ≤ 1.5 mg/dl, aspartate/alanine aminotransferase concentrations ≤ 2 times the upper limit of normal, and serum albumin level ≥ 3 g/dl), and renal function (serum creatinine ≤ 1.5 mg/dl or creatinine clearance ≥ 50 ml/min). Patients with active coronary artery disease (in the form of unstable angina or myocardial infarction over the last 12 months) and/or unstable diabetes mellitus were excluded. Patients with asymptomatic brain metastases controlled with corticosteroids or prior radiotherapy were allowed to participate. All patients were required to sign a written informed consent, and the study was approved by the local ethical committee.

2.2. Treatment

A fixed dose of gemcitabine 1000 mg/m^2 dissolved in 250 ml of 0.9% saline was administered intravenously (iv) over 30 min on days 1 and 8; a fixed dose of cisplatin 70 mg/m^2 dissolved in 500 ml of 0.9% saline was administered iv over 45 min on day 2, according to the standard hydration scheme with at least 2 l of fluids and osmotic diuretics; etoposide dissolved in 250 ml of 0.9% saline was administered iv over 30 min on days 3, 4, and 5 at a starting dose of 50 mg/m^2. All drugs were given every 3 weeks (2 weeks of treatment followed by 1 week of rest). The antiemetic prophylaxis consisted of hydroxytryptamine-3-receptor antagonist plus 20 mg of dexamethasone on day 2.

Sequential thoracic radiation therapy (TRT) in responding limited-stage disease patients was planned after a maximum of 4 cycles; in the event of stable or progressive disease after 2 cycles, they were withdrawn from the study and could received second-line chemotherapy. TRT consisted of 50.4 Gy in 28 fractions (1.8 Gy/day). The initial field included the residual

tumor (if any) with a 1.5 cm margin around the mass, the ipsilateral hilum, the entire width of the mediastinum, and the supraclavicular lymph nodes (if previously involved). For patients with extensive-stage disease who responded or had stable disease, a maximum of 6 cycles of chemotherapy was planned. A prophylactic brain irradiation was planned for all patients with a CR to treatment.

2.3. Dose escalation and adjustment procedures

Three consecutive patients were admitted to each etoposide dose level and 3 weeks had to pass between the inclusion of a patient at each dose level and the following patient. The starting dose of etoposide was 50 mg/m^2, which was escalated in 25 mg/m^2 increments at each level. Dose escalation was continued until more than one-third of the patients in a given cohort developed DLT upon completing the first cycle of treatment, in which case, the dose level immediately below was defined as the MTD and the dose level recommended for subsequent phase II trials. If one DLT occurred in one of the first three patients, three more patients were enrolled at the same dose level. DLT was defined as: (1) ANC $\leq 0.5 \times 10^9$/l over 7 days or $\leq 0.1 \times 10^9$/l over 3 days; (2) platelet count $\leq 25 \times 10^9$/l or $\leq 50 \times 10^9$/l with bleeding; (3) neutropenic fever; or (4) grade 4 non-hematologic toxicity, except nausea/vomiting and alopecia.

In the phase II evaluation, the following dose-adjustment guidelines were followed. On day 8, gemcitabine was omitted if the ANC was $\leq 1 \times 10^9$/l, the platelet count was $\leq 75 \times 10^9$/l, hemoglobin was ≤ 9.5 g/dl, or if the patient experienced a grade 3/4 non-hematologic toxicity (except nausea/vomiting and alopecia). On day 21, if the ANC was $\leq 1 \times 10^9$/l, platelets were $\leq 75 \times 10^9$/l, hemoglobin was ≤ 9.5 g/dl, or the patient experienced a grade 3/4 non-hematologic toxicity (except nausea/vomiting and alopecia), chemotherapy was delayed until recovery, with a maximum delay of 3 weeks, beyond which the patient was withdrawn from the study. The dose of cisplatin was reduced by 50% in the event of grade 2 neurological toxicity or grade 1 renal toxicity. Patients experiencing febrile neutropenia during chemotherapy, grade 4 thrombocytopenia, or $\geq$ grade 3 non-hematologic toxicity (except alopecia) were treated with 75% of the dose for all three drugs, and were returned to full dose if the reduced dose was well tolerated (absence of toxicity).

Radiotherapy, administered as supportive care, was permitted if it did not interfere with measurable disease. The use of G-CSF (filgrastim) was not allowed during the first cycle in the phase I trial, unless in the event of febrile neutropenia. For the subsequent cycles and during the phase II trial it was allowed in case of febrile neutropenia and grade 3–4 not-febrile neutropenia lasting more than 7 days.

2.4. Baseline and follow-up assessments

Before enrollment, a full medical history, physical examination with assessment of performance status, complete blood count (CBC) with differential, full serum chemistry profile, urinalysis, and electrocardiogram (ECG) were performed for each patient. A chest radiograph, bronchoscopy, computed tomography (CT) scan of the chest, the brain, and the abdomen, and radionuclide bone scanning had to be obtained within the month preceding the study entry. For limited stage disease, bone marrow aspiration or biopsy were not required, unless in case of elevated LDH, and/or unexplained thrombocytopenia or leukocytopenia.

Before each cycle, all patients had a complete medical history, physical examination, CBC, full serum chemistry profile, chest radiograph, and ECG. Throughout treatment, CBC was performed weekly; in the event of grade 3/4 neutropenia, thrombocytopenia, or febrile neutropenia, CBC was performed daily until resolution.

All patients who received at least 2 cycles of treatment were evaluable for response and all patients who received at least 1 cycle were evaluable for toxicity. Tumor response was assessed by CT scans every 2 cycles but could be repeated sooner or at any other time if clinically indicated. Toxicity and response were evaluated per standard WHO criteria [10]. The duration of response was measured from the date of documentation of the first response to the date of the first observation of progressive disease. Survival was measured from administration of the first dose to the date of death. Time to progression was measured from administration of the first dose to the first date of documented progressive disease or death from any cause.

The efficacy analyses included tumor response rate calculated on an intent-to-treat basis, with a 95% confidence interval (CI), and Kaplan–Meier estimates for the distributions of overall survival time, time to progression, and duration of response [11].

3. Results

3.1. Patient characteristics

A total of 56 patients were entered into the study from September 1998 to April 2000. The baseline patient characteristics are summarized in Table 1. Most patients were men (78.6%) and had limited-stage disease (66%).

Table 1
Patient characteristics

Characteristic	No. patients	
	$N = 56$	%
Sex		
Male	44	78.6
Female	12	21.4
Age, years		
Median	62	
Range	26–74	
WHO performance status		
0–1	42	75.0
2	14	25.0
SCLC stage		
Limited-stage disease	37	66.1
Extensive-stage disease	19	33.9

WHO, World Health Organization; SCLC, small cell lung cancer.

3.2. Dose escalation results

Dose escalation results are summarized in Table 2. A total of 26 cycles were administered, 24 in the first dose level, and two in the second. A cohort of three patients entered into the first dose level. Because one of the three patients experienced DLT (grade 4 neutropenia with fever), three more patients were added to that dose level. No other DLTs occurred in the six patients, so dose escalation continued. Two patients were included in the second dose level, both of whom experienced DLT: grade 4 neutropenia with fever in the first patient, and grade 4 neutropenia with fever and grade 4 thrombocytopenia, requiring platelet transfusion, in the second patient, who died of sepsis. Therefore, dose escalation was stopped at the second dose level, and the first dose level (gemcitabine 1000 mg/m^2, cisplatin 70 mg/m^2, and etoposide 50 mg/m^2) was considered the MTD. An additional 48 patients were included in the first dose level to further define the toxicity and efficacy of this regimen in the phase II portion of the study ($n = 54$).

3.3. Overall toxicity

Of the two patients treated at etoposide 75 mg/m^2, there were no additional grade 3/4 hematologic toxicities, and no non-hematologic toxicities of any grade level were reported.

Table 3
WHO hematologic toxicity for patients treated with etoposide 50 mg/m^2 ($N = 54$)

Toxicity	Grade 3	Grade 4
Neutropenia	23 (42.6%)	13 (24.1%)
Thrombocytopenia	15 (27.8%)	14 (25.9%)
Anemia	7 (13.0%)	1 (1.9%)
Febrile neutropenia	3 (5.6%)	1 (1.9%)

WHO, World Health Organization.

Table 3 shows the WHO hematologic toxicities that occurred in the 54 patients treated at etoposide 50 mg/m^2 throughout the 233 cycles delivered. A total of 36 (66.7%) patients experienced grade 3/4 neutropenia, but febrile neutropenia occurred in only 4 (7.4%) patients, who were all hospitalized. All neutropenic fevers occurred on day 15 and 26 (48.1%) patients required G-CSF at least once during the course of treatment. The incidence of grade 3/4 thrombocytopenia was slightly less frequent, occurring in 29 (53.7%) patients, but platelet transfusions were required in only three (5.6%) patients. Grade 3/4 anemia occurred in eight (14.8%) patients and required packed red blood cell transfusion in four (7.4%) cases. Thrombocytopenia and anemia occurred on day 15 in more than 80% and 95% cycles, respectively.

Non-hematologic toxicity was generally mild (Table 4). Transient alopecia was common. Nausea and vomiting were frequent but reached grade 3 only in

Table 4
WHO non-hematologic toxicity for patients treated with etoposide 50 mg/m^2 ($N = 54$)

Toxicity	Grade 3	Grade 4
Diarrhea	3 (5.6%)	1 (1.9%)
Nausea/vomiting	3 (5.6%)	0
Fatigue	4 (7.4%)	0
Peripheral neuropathy	1 (1.9%)	0
Dysphagia	1 (1.9%)	0
Neurologic toxicity	2 (3.7%)	0
Pulmonary toxicity	2 (3.7%)	0

WHO, World Health Organization.

Table 2
Results of etoposide dose escalation

Etoposide dose (mg/m^2)	No. patients	DLT	Toxicity type
50	6	1 of 6	Grade 4 neutropenia with febrile neutropenia on day 15
75	2	2 of 2	Grade 4 neutropenia with febrile neutropenia on day 15
			Grade 4 neutropenia with febrile neutropenia, grade 4 thrombocytopenia requiring platelet transfusion on day 11

DLT, dose-limiting toxicity.

three (5.6%) patients, whereas severe diarrhea, the main grade 3/4 non-hematologic toxicity, was observed in four (7.4%) patients. Moderate to severe fatigue was reported in eight (14.8%) cases. Mild renal abnormalities occurred in three patients, whereas grade 3 peripheral neuropathy and grade 2 neurohearing toxicity occurred only in one case. Grade 3 dysphagia and grade 3 pulmonary toxicity (pneumonitis) were reported in one and two patients, respectively, but were transient and recovered rapidly.

In addition to the patient who died from sepsis during treatment at the 75 mg/m^2 etoposide dose level in the phase I evaluation, an additional patient in the phase II evaluation with a performance status of 2 and grade 4 febrile neutropenia, grade 4 thrombocytopenia, and grade 4 diarrhea also died of sepsis after 1 cycle of chemotherapy.

3.4. Dose administration

Each patient who received etoposide 75 mg/m^2 received 1 cycle each, for a total of 2 cycles. The 54 patients who received the lower etoposide dose in the phase II evaluation received 233 cycles. The median number of cycles delivered was 4 and 66% of the patients received at least four courses of chemotherapy. Of these cycles, dose reductions and 1-week delays for all three drugs were necessary in 6.4 and 25.8% of cycles, respectively, whereas omissions of the gemcitabine infusion on day 8 occurred in 12.9% of cycles. Dose reductions for cisplatin, due to neurologic toxicity, were required in 3.4% of cycles.

3.5. Response and survival

The two patients treated at etoposide 75 mg/m^2 were not evaluable for response because of insufficient therapy (<2 cycles of therapy) due to unacceptable toxicity. Thus, no responses were recorded for these patients.

Of the 54 patients who received etoposide 50 mg/m^2 in the phase II evaluation, 46 patients completed at least 2 cycles and were evaluable for response. Eight patients were not evaluable because of insufficient therapy (<2 cycles) due to refusal to continue treatment in three, clinical progression of disease in two, and unacceptable toxicity in three cases. Ten CR and 29 partial responses were recorded for a 72.2% ORR (95% CI, 56.6–85.0%) on an intent-to-treat basis (Table 5). The median duration of response was 8.0 months (range, 3–28 months). Twenty-seven of 36 (75%) patients with limited-stage disease and 12 of 18 (66.7%) patients with extensive-stage disease responded to treatment. The CR in patients with limited-stage disease was 27.8%, whereas no CR was reported in patients with extensive-stage disease.

Thirteen out of 27 responsive patients with limited-stage disease underwent sequential TRT. The remaining 14 patients were deemed not eligible for radiotherapy as a result of persistence of pleural effusion (12 cases) or unfit performance status (2 cases).

After a median follow-up period of 15.5 months (range, 5–28 months), four patients are still alive and two are progression-free. The median time to progression was 8.5 months (8.5 months for patients with limited-stage disease and 6 months for those with extensive-stage disease). Median survival was 10 months without any relevant difference between patients with limited- and extensive-stage disease (10 and 8 months, respectively). The 1-year estimated survival probability is 37.5% (Fig. 1), with a better outcome for limited-stage disease (51.5%) versus extensive-stage disease (31.6%) patients (Fig. 2).

4. Discussion

Although there have been slight improvements in long-term survival for patients with limited-stage SCLC, prognosis for extensive-stage disease remains poor and almost all patients are dead within 24 months of diagnosis [12,13]. Therefore clinical research is focusing on several treatment modalities to improve the outcome of patients with SCLC. High-dose chemotherapy, alternating chemotherapy, and maintenance chemotherapy have been tested, but results are still controversial without any substantial benefit for these patients [14]. The introduction of several new agents with activity against SCLC and favorable toxicity profiles has provided new possibilities to improve treatment. Incorporation of these new agents into standard regimens has been main goal in active clinical research. New agents that have demonstrated relevant activity in phase II studies include topotecan (39%), irinotecan (47%), paclitaxel (34%), gemcitabine (27%), docetaxel (28%), and vinorelbine (27%) [15].

In this phase I study, we have shown that the combination of gemcitabine with cisplatin and etoposide at the dose level recommended for phase II trials (gemcitabine 1000 mg/m^2, etoposide 50 mg/m^2, and cisplatin 75 mg/m^2) is active and feasible in the treatment of SCLC. Dose-limiting toxicities included grade 4 neutropenia with fever and grade 4 thrombocytopenia requiring platelet transfusion. A similar dose-finding study using oral instead of iv etoposide also recommended this regimen for phase II studies [16].

The incidence of non-hematologic side effects in our study was low and although without G-CSF support, the gemcitabine/cisplatin/etoposide triplet produced frequent but tolerable hematologic toxicity, with grade 3/4 neutropenia and thrombocytopenia reported in about two-thirds and more than half of the patients, respec-

Table 5
Response in patients treated with etoposide 50 mg/m^2 ($N = 54$)

	Total ($N = 54$)	SCLC disease stage	
		Limited-stage disease ($n = 36$)	Extensive-stage disease ($n = 18$)
ORR (%)	72.2	75.0	66.7
CR	10	10	0
PR	29	17	12
SD	6	3	3
PD	1	1	0
Not evaluable	8	5	3

SCLC, small cell lung cancer; ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

tively. The clinical sequelae of the hematologic events were infrequent, with only six of 56 (10.7%) patients developing febrile neutropenia, and five of 56 (3.6%) patients requiring platelet transfusions due to thrombocytopenia-associated bleeding. We observed two (3.5%) toxic deaths due to neutropenic sepsis, of which one occurred at the 75 mg/m^2 etoposide dose level. This treatment-related death rate, which ranges from 3 to 8%, is consistent across most phase II/III studies enrolling patients with extensive-stage disease [17–19].

The addition of the new agent, paclitaxel, to a platinum and etoposide regimen has been studied extensively over the last several years. Two large phase II studies have tested the combination of paclitaxel, cisplatin, and etoposide in patients with extensive SCLC. In the first trial, Glisson et al. [17] defined a paclitaxel MTD of 130 mg/m^2 in combination with cisplatin 75 mg/m^2 and 3-day etoposide 80 mg/m^2; 38 patients were treated at this dose level. The objective response rate was 90%, with a CR of 16%, and median survival was 10.9 months. Kelly et al. [18] combined paclitaxel 175 mg/m^2 with cisplatin 80 mg/m^2 and etoposide 80 mg/m^2 iv on day 1 followed by a 2-day oral etoposide schedule at 160 mg/m^2. The objective response rate was 56% among 82 evaluable patients, and the median survival was 11 months. In both trials, neutropenia was the main toxicity. In the first trial, which did not allow the use of G-CSF, neutropenia occurred in about half of the patients but without any febrile neutropenia. In the second trial, which scheduled 11 days of G-CSF support, neutropenia occurred in 35% of the patients. Toxic deaths were common in both studies, 5 and 7%, respectively.

The results of a randomized trial comparing paclitaxel/cisplatin/etoposide regimen (paclitaxel 175 mg/m^2 on day 1, cisplatin 80 mg/m^2 on day 2, and etoposide 80 mg/m^2 on days 2–4, every 28 days) with the standard cisplatin/etoposide regimen (cisplatin 80 mg/m^2 on day 1 and etoposide 120 mg/m^2 iv on days 1–3, every 28 days) were recently reported by Mavroudis et al. [19]. Due to excessive treatment-related mortality in the paclitaxel-containing arm (8 deaths/62 patients), the study was closed early after an interim analysis. Despite G-CSF support, the investigational arm was associated with significantly more severe neutropenia, thrombocytopenia, and febrile neutropenia. A longer time to disease

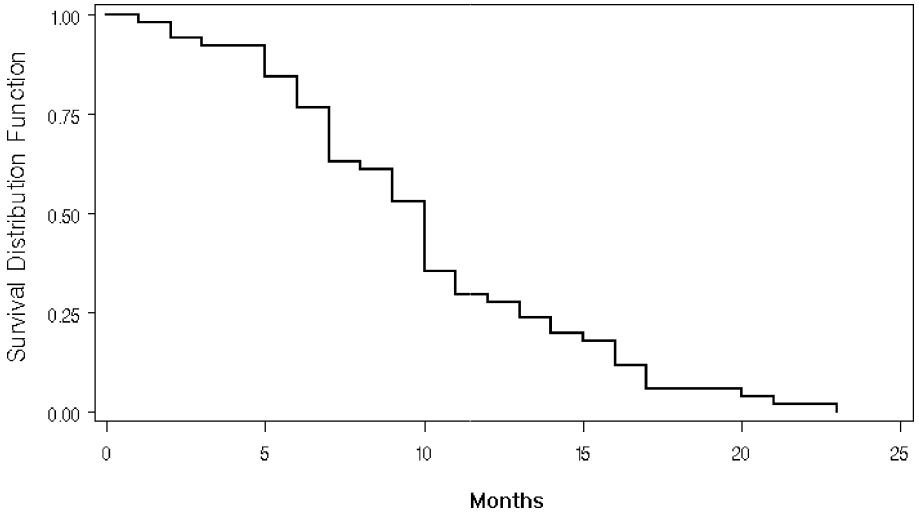

Fig. 1. Overall survival ($N = 54$).

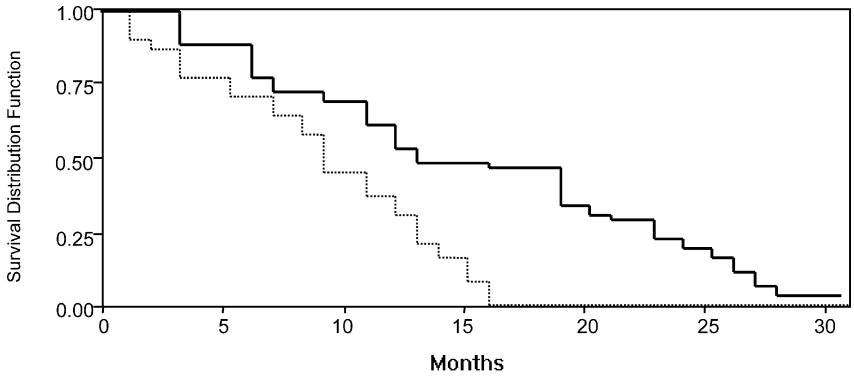

Fig. 2. Overall survival by extent of disease. Limited disease (—); extensive disease (· · · ·).

progression was found in favor of the triplet regimen (11 months vs. 9 months, $P = 0.02$), but ORR, 1-year survival, and overall survival were similar in the two arms.

Currently, several regimens integrating paclitaxel with carboplatin and etoposide or topotecan have shown to be highly active and feasible in 3 phase II studies, with response rates of 65–88% in patients with extensive disease and acceptable toxicity. A high-dose regimen of paclitaxel/carboplatin/etoposide consisting of carboplatin AUC = 6 and paclitaxel 200 mg/m^2 (oral etoposide 50 mg/m^2 alternated with 100 mg/m^2 for 10 consecutive days) was more effective than the low-dose regimen using carboplatin AUC = 5 and paclitaxel 135 mg/m^2 with a response rate of 84 versus 65% and a median survival time of 10 versus 8 months ($P = 0.04$ for survival). The high-dose regimen was administered at full-dose with acceptable toxicity. The toxicity was similar between the two regimens, especially in terms of febrile neutropenia and grade 4 neutropenia. Growth factor support was not scheduled [20,21].

In a randomized, phase III study in 373 evaluable patients so far, the ORR of patients treated with paclitaxel, carboplatin, and etoposide was 93% compared to 87% for patients treated with vincristine, carboplatin, and etoposide. The hematologic toxicities, thrombocytopenia and anemia, occurred less frequently in the paclitaxel arm [22].

5. Conclusions

In the current study, the ORR to the combination of cisplatin and etoposide with the novel agent gemcitabine was 72% in 46 evaluable patients; 67% of the 18 patients with extensive-stage disease and 75% of the 36 patients with limited-stage disease responded to treatment. Median time to progression was 8.5 months, and median survival was 10 months without any relevant difference between patients with limited-stage and extensive-stage disease in either endpoint (8.5 and 6 months for time to progression; 10 and 8 months for median survival). These results are similar to those obtained by others investigators using paclitaxel-based regimens, particularly in extensive-stage disease. The differences noted between patients with limited-stage and extensive-stage disease should be interpreted with caution, however, as the demarcation line between the disease states is often unclear, depending on local practices.

The role of gemcitabine, as well as other new agents, in the treatment of SCLC continues to be clarified. As discussed, several regimens incorporating a new drug to the platinum/etoposide combination, including the 3-drug regimen evaluated in this study, have demonstrated activity similar to that of the best previous regimens with tolerable toxicity. In some instances, combination chemotherapy including novel agents has actually improved objective responses as well as survival [23,24], but this promising outcome needs confirmation in large, well-controlled clinical trials.

We are currently conducting a large randomized trial comparing the current triplet regimen with gemcitabine/cisplatin, as clinical research in SCLC has been exploring the activity of etoposide-free regimens such as irinotecan/cisplatin [25], gemcitabine/cisplatin [26], and carboplatin/paclitaxel [27]. The study has reached the planned accrual, and results are eagerly awaited. Irinotecan/cisplatin, the first of these regimens to be compared with the standard cisplatin/etoposide regimen in a randomized study, showed a significant advantage in terms median survival with acceptable toxicity [25].

References

[1] Bunn PA, Jr, Carney DN. Overview of chemotherapy for small cell lung cancer. Semin Oncol 1997;24(2 Suppl. 7):69–74.
[2] Johnson DH. Management of small cell lung cancer: current status of the art. Chest 1999;116:525–30.
[3] Zochbauer-Muller S, Pirker R, Huber H. Treatment of small cell lung cancer patients. Ann Oncol 1999;10(Suppl. 6):83–91.

[4] Storniolo AM, Allerheiligen S, Pearce HL. Preclinical, pharmacologic and phase I studies of gemcitabine. Semin Oncol 1997;24(2 Suppl. 7):2–7.
[5] Cormier Y, Eisenhauer E, Muldal A, et al. Gemcitabine is an active new agent in previously untreated extensive-stage small cell lung cancer (SCLC). A study of the National Cancer Institute of Canada Clinical Trials Group. Ann Oncol 1994;5:283–5.
[6] Peters GJ, Bergman AM, Ruiz van Haperen VW, et al. Interaction between cisplatin and gemcitabine in vitro and in vivo. Semin Oncol 1995;22(4 Suppl. 11):72–9.
[7] Rosell R, Tonato M, Sandler A. The activity of gemcitabine plus cisplatin in randomized trials in untreated patients with advanced non-small cell lung cancer. Semin Oncol 1998;25(4 Suppl. 9):27–34.
[8] van Moorsel CJ, Pinedo HM, Veerman G, et al. Combination chemotherapy studies with gemcitabine and etoposide in non-small cell lung and ovarian cancer cell lines. Biochem Pharmacol 1999;57:407–15.
[9] Rassmann I, Thodtmann R, Depenbrock H, et al. Gemcitabine and etoposide in small cell lung cancer: phase I and II trials. Semin Oncol 1997;24(2 Suppl. 7):75–8.
[10] Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981;47:207–14.
[11] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
[12] Ihde DC, Mulshine JL, Kramer BS, et al. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. J Clin Oncol 1994;12:2022–34.
[13] Murray N, Coy P, Pater JL, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1993;11:336–44.
[14] Aisner J. Extensive-disease small-cell lung cancer: the thrill of victory; the agony of defeat. J Clin Oncol 1996;14:658–65.
[15] Ettinger DS. New drugs for chemotherapy-naive patients with extensive-disease small cell lung cancer. Semin Oncol 2001;28(2 Suppl. 4):27–9.
[16] Stewart DJ, Earle C, Cormier Y, et al. Phase I study of cisplatin, etoposide and gemcitabine in small cell lung cancer. Proc Am Soc Clin Oncol 1997;16 (abstr. 1627).
[17] Glisson BS, Kurie JM, Perez-Soler R, et al. Cisplatin, etoposide, and paclitaxel in the treatment of patients with extensive small-cell lung carcinoma. J Clin Oncol 1999;17:2309–15.
[18] Kelly K, Bunn PA, Lovato L, et al. Final results from Southwest Oncology Group trial (SWOG) 9705: A phase II trial of cisplatin, etoposide and paclitaxel (PET) with G-CSF in untreated patients with extensive stage small-cell lung cancer. Proc Am Soc Clin Oncol 2000;19 (abstr. 1923).
[19] Mavroudis D, Papadakis E, Veslemes M, et al. A multicenter randomized clinical trial comparing paclitaxel-cisplatin-etoposide versus cisplatin-etoposide as first-line treatment in patients with small-cell lung cancer. Ann Oncol 2001;12:463–70.
[20] Hainsworth JD, Gray JR, Stroup SL, et al. Paclitaxel, carboplatin and extended-schedule etoposide in the treatment of small-cell lung cancer: comparision of sequential phase II trials using different dose-intensities. J Clin Oncol 1997;15:3464–70.
[21] Hainsworth JD, Burris HA, III, Greco FA. Paclitaxel-based three-drug combinations for the treatment of small-cell lung cancer: a review of the Sarah Cannon Cancer Center experience. Semin Oncol 2001;28(2 Suppl. 4):43–7.
[22] Gatzemeier U, von Pawel J, Macha H, et al. A phase III trial of taxol, etoposide phosphate and carboplatin (TEC) versus carboplatin, etoposide phosphate and vincristine (CEV) in previously untreated small-cell lung cancer. Proc Am Soc Clin Oncol 2000;19 (abstr. 1889).
[23] Bunn PA, Kelly K. New combinations in the treatment of lung cancer: a time for optimism. Chest 2000;117(Suppl. 1):138–43.
[24] Kelly K. New chemotherapy agents for small cell lung cancer. Chest 2000;117(Suppl. 1):156–62.
[25] Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 2002;346:85–91.
[26] Israel VP, Chansky K, Gandara D. Southwest Oncology Group trial (SWOG) S9718: a phase II study of gemcitabine plus cisplatin in patients with extensive small cell lung cancer (E-SCLC). Proc Am Soc Clin Oncol 2001;20 (abstr. 1262).
[27] Thomas P, Castelnau O, Paillotin D, et al. Phase II trial of paclitaxel and carboplatin in metastatic small-cell lung cancer: a Groupe Francais de Pneumo-Cancerologie study. J Clin Oncol 2001;19:1320–5.