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Cisplatin, doxorubicin, cyclophosphamide, and etoposide combination chemotherapy for small-cell lung cancer

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Summary. Because of potential synergistic interactions, we added 25 mg/m^2 i.v. cisplatin (P) 25 given on days 1–5 to the combination of 45 mg/m^2 i.v. doxorubicin (A) given on day 1, 800 mg/m^2 i.v. cyclophosphamide (C) given on day 1, and 50 mg/m^2 i.v. etoposide (E) given on days 1–5. The resulting PACE regimen was given every 21 days for the first three courses and then every 28 days for the next five courses. PACE was used in two trials: the first, for both limited and extensive disease, was conducted at the University of Maryland Cancer Center and North Shore University Hospital; and the second, for extensive disease, was carried out as a Cancer and Leukemia Group B pilot study. Chest irradiation was not used. Prophylactic cranial irradiation at a dose of 3,000 cGy was given to all patients achieving a complete response (CR). A total of 33 subjects were entered in the first study; 8 of the 15 (53%) presenting with limited disease and 7 of the 18 (39%) exhibiting extensive disease achieved a CR. A partial response (PR) was obtained in 27% and 33% of cases, respectively. Of the 34 patients entered in the second study, 25 were eligible; 8 (32%) achieved a CR and 6 (24%) showed a PR. Toxicity was severe in both studies, including >90% severe or life-threatening leukopenia and thrombocytopenia. Serial creatinine-clearance evaluations in the first study indicated progressive deterioration, which required discontinuation of the cisplatin before the planned completion of treatment in most cases. Since the response rate was no higher than the historic data reported for the three-drug ACE combination and because the toxicity was severe, the studies were stopped and patients were followed for survival. After a follow-up period of >6 years, the median survival was 24 months for limited disease, with 33% and 27% of the patients being alive at 3 and 6.5 years, respectively. The median survival for extensive disease was 15 and 11 months in the first and second studies, respectively. These pilot studies suggest that the addition of cisplatin may augment the activity of the ACE regimen, but at the cost of severe toxicity. Further studies seem warranted if the myelotoxicity can be better controlled.

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Introduction

Small-cell lung cancer (SCLC) has received considerable attention in the last decade, in part because of its unique clinical behavior, fulminant clinical course, early dissemination, and sensitivity to both chemotherapy and radiotherapy [7, 8]. In view of the recognized systemic nature of SCLC, chemotherapy is the basic treatment approach [3]. There are numerous agents that show antitumor activity, and a large number of combinations of these drugs have been tested [5]. Combinations of agents that interact synergistically have been advocated to optimize the use of chemotherapy in many cancers, and this approach may be very important in responsive tumors. The potentially synergistic three-drug combination (ACE) of doxorubicin (A), cyclophosphamide (C), and etoposide (E) has been shown to be highly active against both limited and extensive disease [2, 5, 11]. Sequential studies of this three-drug combination in the absence of chest irradiation at the University of Maryland Cancer Center (UMCC) showed a consistently high complete response rate and prolongation of survival, but neither the addition of immunotherapy with the methanol-extracted residue of bacille Calmette-Guérin (BCG) nor the use of either alternating chemotherapy regimens or higher-dose continuous-infusion etoposide produced an improvement over the results obtained using the ACE combination alone [2, 5]. On the bases of evidence for the role of cisplatin (P) in SCLC [1] and its potential synergistic interactions with etoposide [13] as well as the other agents, we added cisplatin to the three-drug ACE regimen and tested this four-drug PACE regimen in the absence of chest irradiation in both limited and extensive

Table 1. Dose and schedule of PACE chemotherapy

Drug	Dose and schedule
Cisplatin (P)	20 mg/m² i. v., days 1–5
Doxorubicin (A)	45 mg/m² i. v., day 1
Cyclophosphamide (C)	800 mg/m² i. v., day 1
Etoposide (E)	50 mg/m² i. v., days 1–5

Table 2. Patients' characteristics

	Disease stage		
	Study I		Study II
	Limited	Extensive	Extensive
Patients (*n*)	15	18	25
Men/women (*n*)	11/4	14/4	17/8
Median age (years)	58	57	57
Range (years)	44–76	40–74	37–70
PS 0/1 (*n*)	5/8	6/4	8/11
PS 2/3/4 (*n*)	0/1/1	6/1/1	1/1/1
Number of CRS (%)	8(53)	7(39)	8/25(32)[a]
Number of PRS (%)	4(27)	6(33)	6/25(24)[a]
Median survival (months)	24.0	15.0	11.0
Number (%) alive at 3 years	5(33)	1(6)	0
Number (%) alive at 5 years	4(27)	0	0

[a] Including 3 patients who were unassessable for response
PS, Performance status; CR, complete response; PR, partial response

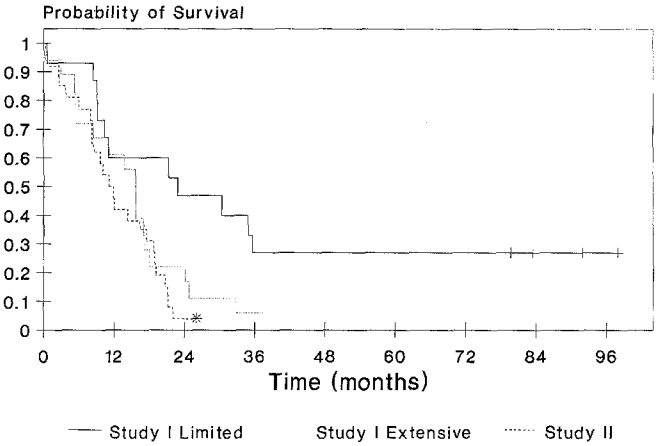

Fig. 1. Final survival curves for both studies: the initial limited- and extensive-disease pilot study and the subsequent CALGB extensive-disease-only trial. The median survival of the 15 patients displaying limited disease is 24 months; that of the 18 subjects exhibiting extensive disease in study I is 15 months, and that of those presenting with extensive disease in study II is 11 months. Four of the patients suffering from limited disease remain disease-free beyond the minimal follow-up period of 6 years.

disease. Two separate studies were performed: the initial trial was conducted at the UMCC and North Shore University Hospital (NSUH), and the subsequent trial in extensive disease was carried out as a Cancer and Leukemia Group B (CALGB) pilot study. The preliminary results of this study have previously been reported [5, 6]. We report herein the final results of both pilot studies.

Patients and methods

For the initial study, sequential patients at UMCC and NSUH were aggressively staged to define the extent of disease. Staging tests included a complete history and physical examination, computerized tomographic (CT) scans of the brain and chest (including the liver, spleen, and adrenal glands), bilateral bone marrow aspirations and biopsies, bronchoscopy, isotopic bone scans, and blood and urine tests for hematologic, renal, and hepatic function. Blood and urine tests included determinations of serum electrolytes, SGOT, SGPT, lactic dehydrogenase (LDH), creatinine clearance, and white blood cell (WBC) and platelet counts with differentials. After staging evaluation, patients were categorized as having either limited or extensive disease. Limited disease was defined as all malignancy that was confined to one hemithorax in the presence or absence of mediastinal involvement. Subjects exhibiting isolated pleural effusions, whether cytologically positive or not, were considered to have limited disease. This definition of pleural effusions was based on a report by the Southwest Oncology Group [12], which suggested that the outcome of patients presenting with isolated pleural effusions was more favorable, and chest irradiation was not planned. Extensive disease was defined as all malignancy located beyond the confines of limited disease.

To be eligible to participate in the study, all patients were required to have histologically confirmed limited- or extensive-stage SCLC; to give their signed informed consent, including an explanation of alternative therapies; and to exhibit a creatinine clearance of >60 ml/min. Normal hepatic function (<1.5 times the normal values for LDH, SGOT, and SGPT) and normal hematologic function (WBC, >3,500/μl; platelets, >100,000/μl) were also required unless the abnormal functions were attributable to documented organ involvement with SCLC. There was no performance-status restriction for patient entry, similar to prior UMCC studies.

The dose and schedule of PACE chemotherapy for the first study are given in Table 1. Courses were repeated every 21 days for the first three courses and were adjusted for renal toxicity as judged by creatinine clearance or for leukopenic sepsis. Evaluations of creatinine clearance were performed before each course of therapy. The subsequent five courses were given every 28 days and were adjusted by 20% for leukocyte nadir and creatinine clearance. Staging reevaluation was performed after the initial three courses and included at the minimum all positive initial staging tests as well as repeat bronchoscopy for all complete responses. Radiotherapy to the chest was not included. For the second CALGB study, only patients exhibiting extensive disease were eligible for inclusion. In this study, renal function was assessed according to serum creatinine levels rather than to 24-h clearance. The dose and schedule of PACE chemotherapy were otherwise similar.

Pretreatment hydration in both studies consisted of at least 1 l normal saline given at 1 h before treatment. Antiemetics generally comprised combinations of metoclopramide, steroids, (e. g., dexamethasone), and a hypnotic such as lorazepam. Following chemotherapy, hydration with at least 1 l normal saline was continued until nausea and vomiting had been well controlled.

Standard CALGB response criteria were used. Briefly, a complete response (CR) was defined as the complete disappearance of all signs and symptoms of disease (including negative bronchoscopy in the first study) and the normalization of bone scans for a minimum of 1 month. A partial response (PR) was defined as a decrease of >50% in the product of the greatest cross-perpendicular dimensions of all indicator lesions and the absence of new lesions or of regrowth of other lesions for at least 1 month. All patients who achieved a CR received prophylactic cranial irradiation of a dose of 3,000 cGy delivered in ten fractions.

Results

A total of 33 eligible patients were entered in the first study, of whom 15 presented with limited disease and 18, with extensive disease. Among the 15 subjects exhibiting limited disease, 3 displayed isolated pleural effusions; 2 showed cytologic evidence of involvement, and the effusion in the other case was cytologically negative. All patients suffering from extensive disease exhibited two or more sites of extrathoracic involvement. In all, 34 individuals were entered in the second CALGB trial. Exclusion of patients from this study presented a problem. Two entries were canceled prior to the study and seven were ineligible as follows: three patients had only limited disease and were eligible for other limited-disease studies; three displayed histologies other than SCLC; and in one case, no prestudy or follow-up data were available. Thus, 25 patients were eligible for the second, extensive-disease-only trial, and all displayed ≥ 2 sites of extrathoracic disease. The characteristics, response, and median survival of all subjects are shown in Table 2. The CR rate for limited disease was 53%, and that for extensive disease was 39% and 32% for the first and second studies, respectively. The minimal follow-up period is currently >6 years. The survival curves for the first and second trials are shown in Fig. 1. The median duration of survival for limited disease was 24 months; 5 of the 15 (33%) patients were alive at 3 years, and 4 (27%) are alive at ≥ 6 years. For extensive disease, the median duration of survival was 15 and 11 months for the first and second studies, respectively.

In both studies, PACE chemotherapy was moderately tolerated, with uniform nausea, vomiting, alopecia, and severe myelosuppression being observed. Aggressive hydration, antiemetics, and hospitalization were required for nearly all courses. In the first study, the median WBC nadir was $0.5 \times 10^3/\mu l$ (range, $0-1.1 \times 10^3/\mu l$), and the median platelet nadir was $16 \times 10^3/\mu l$ (range, $11-89 \times 10^3/\mu l$). Among the 33 patients, there were 21 infectious episodes and 2 septic deaths, both of which involved subjects whose initial CALGB performance status was 3 or 4. Sequential creatinine-clearance studies indicated a progressive deterioration in renal function with the increasing number of courses given. Deterioration of renal function or neuropathies required discontinuation of cisplatin prior to the completion of all courses of therapy in 22 of the 33 patients, and a median of 5 of the 8 planned cisplatin-containing courses were completed.

Toxicities in the CALGB extensive-disease study were similar, with 92% of the subjects developing severe or life-threatening leukopenia (9% severe and 83% life-threatening) and 92% developing thrombocytopenia (35% severe an 57% life-threatening). Other severe plus life-threatening toxicities included: anemia, 73%; febrile episodes, 21%;, infectious episodes, 43%; nausea and vomiting, 26%; hemorrhage, 8%; stomatitis, 9%; and neuropathies, 8%. No toxic death occurred in this group.

Discussion

The two studies using PACE combination chemotherapy alone for SCLC were conducted sequentially. Initially, this project was a two-institution study in limited and extensive disease. When the PACE combination was adopted for use in a CALGB extensive-disease study, UMCC and NSUH continued their initial study in limited disease while participating in the CALGB extensive-disease study. Patients exhibiting isolated pleural effusions were included among those presenting with limited disease due to reports of a more favorable outcome for such individuals [12] and because chest irradiation was not included. Placement of these subjects in the extensive-disease group would have introduced a favorable bias for that group. All patients in the first study were assessable. The exclusion rate in the CALGB study was somewhat higher than usual, but most of the subjects who were disqualified displayed either the wrong stage of disease ($n = 3$) or inappropriate histologies ($n = 3$) at the review. After an interim analysis of the data from both studies had shown a response rate similar to that reported in previous UMCC three-drug ACE studies [5, 6], the two PACE studies were stopped and the patient were followed for survival. However, the final analysis of these studies is of some interest.

The two studies show some overlap, especially with respect to extensive disease, but a comparison of the trials would not be appropriate. Furthermore, due to the small numbers of patients entered in each of the studies, any conclusion would be only tentative. Nevertheless, the first study appears to be remarkable in that the median and long-term survival for both limited and extensive disease in the UMCC/NSUH study seem to be better than our historic data for ACE chemotherapy [2, 5]. The apparent increase observed in the duration of survival despite the lack of an apparent increase in the CR rate is a matter of some concern, especially since our early stopping policies in the treatment of this disease at UMCC have focused on the CR frequency [4]. The present CALGB extensive-disease trial also suggests a possible increase in the CR rate and in median survival as compared with the results of prior CALGB extensive-disease studies.

Despite the encouraging results obtained in the two pilot studies, several concerns limit the immediate reexploration of this regimen. First, a somewhat similar study by Scullier et al. [14] achieved similar response rates, but the survival of patients in that investigation appeared to be less encouraging. The reason for this discrepancy, between the two studies is not apparent. Second, despite a reduction in the cyclophosphamide dose, the addition of cisplatin to the ACE combination resulted in enhanced toxicity as compared with the ACE data. For example, most of the PACE chemotherapy required hospitalization of the patients either during or between courses or both, whereas the ACE regimen was mostly given on an ambulatory basis. Finally, the results than can be achieved using less aggressive chemotherapy and chest irradiation [1, 9] for limited disease and the eventual treatment failure despite extremely aggressive chemotherapy for patients suffering from extensive disease [10] must presently limit the application of the PACE regimen in view of the resulting toxici-

ties. However, the current studies do suggest that cisplatin may interact synergistically with one or more of the agents in the PACE regimen. Further studies using this regimen, even at escalated doses, may therefore be of considerable interest if toxicities such as myelosuppression can be more effectively controlled. One potential approach might involve the use of colony-stimulating factors that allow for both myeloid and megakaryocytic stimulation.

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