Evaluation of Cisplatin, Carboplatin, and Etoposide in Metastatic Nonsmall Cell Lung Carcinoma

A Phase II Study of the Southwest Oncology Group

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Supported in part by the following PHS Cooperative Agreement grant numbers awarded by the National Cancer Institute, DHHS: CA58348, CA37981, CA45560, CA28862, CA27057, CA35431, CA35200, CA58686, CA13612, CA12644, CA35281, CA52654, CA58861, CA45377, CA46441, CA52772, CA46113, CA46282, CA38926, and CA32102.

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Received January 18, 1996; revision received May 14, 1996; accepted June 3, 1996.

BACKGROUND. The combined use of cisplatin and carboplatin chemotherapy offers a unique means of platinum dose intensification. Response rates using either of these agents in combination with etoposide are comparable. In a Phase II trial, the authors investigated the combination of cisplatin and carboplatin with etoposide for the treatment of patients with advanced nonsmall cell lung carcinoma.

METHODS. Eligible patients were chemotherapy naive and had histologically confirmed, evaluable, or measurable selected Stage IIIB and Stage IV nonsmall cell lung carcinoma. Based upon the results of an earlier Phase I and II pilot study, patients received carboplatin, 225 mg/m^2, on Day 1; cisplatin, 50 mg/m^2, on Days 2 and 3; and etoposide, 75 mg/m^2, on Days 1, 2, and 3 every-4-weeks.

RESULTS. Eighty-three patients (75 eligible patients) received chemotherapy with cisplatin, carboplatin, and etoposide. Two patients refused therapy after registration and were not analyzable. Thirty-six of the remaining 75 patients had Grade 4 toxicities, mostly hematologic, and 6 patients died of toxicity. The confirmed response rate was 24% (95% confidence interval, 15–35%). Median progression-free survival was 4 months and the median survival was 8 months.

CONCLUSIONS. Combination cisplatin, carboplatin, and etoposide chemotherapy appears to be no better than cisplatin/etoposide or carboplatin/etoposide for the treatment of patients with nonsmall cell lung carcinoma. The toxicity of this regimen may be higher, and therefore it cannot be recommended for general use.
***Cancer* 1996; 78:998–1003.**

KEYWORDS: lung carcinoma, cisplatin, carboplatin, etoposide, chemotherapy.

Patients with metastatic nonsmall cell lung carcinoma have median survivals that range from 15 to 25 weeks in most modern series, with 1-year survival in the range of 10–20%.[1] A variety of combination chemotherapy regimens have been shown to be active in nonsmall cell lung carcinoma.[2–4] Cisplatin is one of the most active single agents, with a response rate of 15–20%, with conflicting data regarding higher response rates observed with increasing doses of cisplatin.[4] Carboplatin has also been evaluated in nonsmall cell lung cancer with response rates of 9–16% as a single agent in previously untreated patients with advanced disease.[2,3,5] A randomized study comparing either carboplatin or cisplatin in combination with etoposide resulted in objective response rates of 16% and 27%, respectively, in previously untreated patients.[6]

Recently, there has been an interest in therapy combining cisplatin and carboplatin as a means of escalating the effective dose of platinum-based chemotherapy. Cisplatin and carboplatin have different pharmacokinetics and dose-limiting toxicities. The combination

of cisplatin and carboplatin may therefore have a superior therapeutic index.[7,8] Cisplatin is considerably more likely to lead to nephrotoxicity, neurotoxicity, nausea, and vomiting, whereas myelosuppression is dose-limiting for carboplatin. The pharmacology of cisplatin and carboplatin also differ. Cisplatin is highly protein bound and its active moiety is cleared by nonrenal mechanisms.[9] Conversely, carboplatin is protein bound to a substantially lesser extent and is highly dependent on renal mechanisms for clearance.[10] The molecular species formed when either cisplatin or carboplatin react with DNA is a similar bidentate, N-7-deoxy (GPG) guanine-guanine intrastrand adduct. However, the rate at which cisplatin and carboplatin react with DNA is different, suggesting differences in intracellular pharmacodynamics.[11,12]

A limited number of cell lines and murine tumors have been described in which cisplatin and carboplatin are not completely cross-resistant.[13–15] Furthermore, a prospectively randomized trial comparing cisplatin and carboplatin as primary therapy for ovarian carcinoma showed a 15–20% crossover response rate to carboplatin after disease progression on cisplatin.[16] Further rationale for combining cisplatin and carboplatin may be derived from the evidence supporting a steep dose-response curve for both cisplatin and carboplatin,[17,18] and the advantage that using moderate doses may avoid the chronic toxicities prohibiting further treatment that have been associated with high dose cisplatin, including renal, auditive, and neurologic toxicities.

Several Phase I/II studies have evaluated the combination of cisplatin and carboplatin.[19–21] Trump et al. studied sequential infusions of carboplatin and then cisplatin, showing thrombocytopenia and leukopenia to be the dose-limiting toxicities of the combination. Nausea and vomiting were similar to that observed with cisplatin alone and there was no clinically significant nephrotoxicity, ototoxicity, peripheral neuropathy, nor other limiting or unusual toxicities observed with this combination.[19]

A Phase I/II study was initiated at the University of California at Los Angeles to assess the efficacy and toxicity of cisplatin and carboplatin combination chemotherapy with etoposide in previously untreated patients with advanced, measurable nonsmall cell lung carcinoma.[22] This trial established the maximum tolerated doses and the dose-limiting toxicities of the combination as leukopenia and thrombocytopenia. The objectives of the current trial were to assess the survival and response rates of cisplatin/carboplatin/etoposide combination chemotherapy in patients with selected Stage IIIB and Stage IV nonsmall cell lung cancer. The qualitative and quantitative toxicities of this combination were also evaluated.

PATIENTS AND METHODS

Patient Selection

Criteria for study entry was comprised of histologically confirmed advanced (T4 by the presence of a malignant pleural effusion) Stage IIIB or metastatic (M1) Stage IV nonsmall cell lung cancer. All patients had bidimensionally measurable or evaluable disease outside of any prior radiation field. Evaluable disease included unidimensionally measurable lesions, masses with margins not clearly defined, palpable lesions with either diameter less than 2 cm, any lesion with both diameters less than 0.5 cm, and bone disease. Malignant pleural effusions did not constitute measurable or evaluable disease. Patients with a history of brain metastases were ineligible. Patients must not have received prior chemotherapy or biologic therapy. Patients were permitted to have received prior radiation therapy that must have been completed at least 4 weeks prior to initiation of chemotherapy. All patients had adequate renal (creatinine $\leq$ 1.2 mg% or creatine clearance $\geq$ 65 mL/min) and hepatic function and a Southwest Oncology Group (SWOG) performance status of 0-2 by history. These criteria are standard for advanced nonsmall cell lung cancer trials in SWOG using cisplatin. All patients had absolute granulocyte counts of $\geq$1500/μL and platelet counts of $\geq$150,000/μL. Patients were classified by disease status (measurable vs. evaluable) and by performance status (0–1 vs. 2). Signed informed consent was obtained for all patients. The protocol was approved by SWOG and by the institutional review boards of all participating institutions.

Treatment Schedule

The dose and schedule of chemotherapy was based upon a pilot Phase I/II study[22] initiated in 1989 and included; carboplatin, 225 mg/m^2, administered by intravenous piggyback (IVPB) in 100 mL NS over 30 minutes on the first day of each 4-week cycle; etoposide, 75 mg/m,^{2} administered by IVPB in 500 mL NS over 2 hours on Days 1, 2, and 3 of each 4-week cycle; and cisplatin, 50 mg/m^2 administered by IVBP infusion on Days 2 and 3 of each 4-week cycle. Cisplatin was administered on an outpatient basis. Standard intravenous hydration and antiemetics were used. Chemotherapy was repeated every 4 weeks for up to 6 cycles. Nonresponding patients received a minimum of two cycles or until progression of disease. Responding patients received a maximum of six cycles. Patients were removed from the protocol for progression of disease at any time, unacceptable toxicity, or patient refusal

to continue therapy. Standard dose reductions were incorporated for hematologic and nonhematologic toxicities. Dose reductions for hematologic toxicity was based on nadir counts after the preceding course. If the leukocyte count was < 3500 or the platelet count was < 125,000 on Day 1 of cycle, treatment was delayed until recovery and then reduced to carboplatin, 165 mg/m^2 for a leukocyte count between 1000–1499 or platelet count between 25,000–49,000, or carboplatin, 110 mg/m^2, for a leukocyte count of < 1,000 or platelet count of < 25,000 for nonhematologic toxicities. A 50% dose reduction of cisplatin was incorporated for Grade 3 gastrointestinal toxicity, renal toxicity with creatinine > 1.3, and Grade 2 neurologic/central nervous system toxicity.

Response and Toxicity Criteria

Response and toxicity were graded according to standard SWOG criteria.[23] Complete response was defined as complete resolution of all measurable and evaluable disease and the appearance of no new lesions for a period of at least 4 weeks. Partial response was defined as a ≥50% decrease under baseline in the sum of the products and perpendicular diameters of all measurable lesions with no progression of evaluable lesions for at least 4 weeks. Progressive disease was defined as a 25% increase in the sum of the products of the measurable lesions over the smallest sum observed, or the appearance of new lesions. Stable disease was defined as disease not qualifying for classification as complete response, partial response, or progression.

Statistical Methods

This study was designed for a single stage of accrual. Progression free survival was defined as the time of registration to the time of progression or last contact, and survival was defined as the time from registration to last contact. Both were estimated using the product-limit method,[24] with patients who were alive at last contact treated as censored. The confidence interval (CI) for the response rate was calculated by the exact method.

RESULTS

Patient Characteristics

Between August 1991 and March 1992, 83 patients from SWOG institutions were registered. Six patients (7%) were ineligible and excluded from the analyses. Four patients did not have the correct stage of disease (three did not have metastatic disease, and one had brain metastasis), and two had baseline laboratory measurements taken outside the required time constraints. Two patients refused treatment after registration and were not analyzable. Table 1 describes the patient characteristics.

TABLE 1
Patient Characteristics

	No (%)
Age (yrs)	
Median	60
Range	38–77
Sex	
Male	53 (71)
Female	22 (29)
Performance Status	
0–1	55 (73)
2	20 (27)
Disease	
Measurable	64 (85)
Evaluable	11 (15)

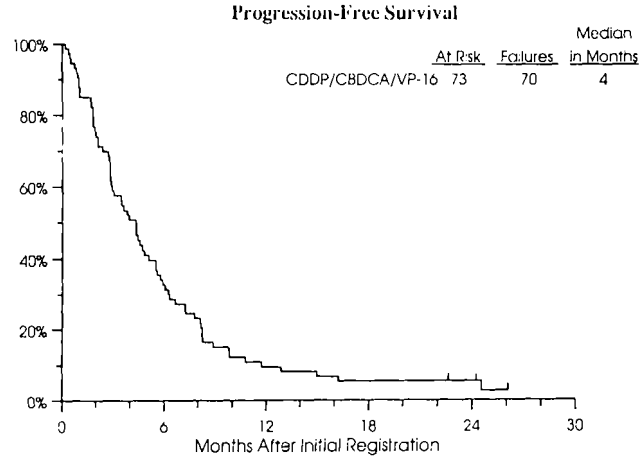

FIGURE 1. Progression free survival of patients in study.

Seventy-five patients were analyzed for treatment efficacy and toxicity. Eleven patients completed 6 courses of therapy as planned. Twenty-nine patients discontinued therapy due to progression or relapse, 20 patients due to toxicity or side effects, and 8 due to death. Seven patients were taken off treatment for reasons not protocol-specified. There were no major protocol violations.

Response assessment was determined in 75 patients. There were 18 responses 3 complete, 11 partial, and 4 partial nonmeasurable disease) for a confirmed response rate of 24% (95% CI, 15–35%). Sixteen responses (29%) and 2 responses (10%) were observed in Eastern Cooperative Oncology Group (ECOG) 0,1 versus 2 patients, respectively. Twenty-four patients had stable disease (32%), 15 had progressive disease (20%), and 4 died before response could be assessed

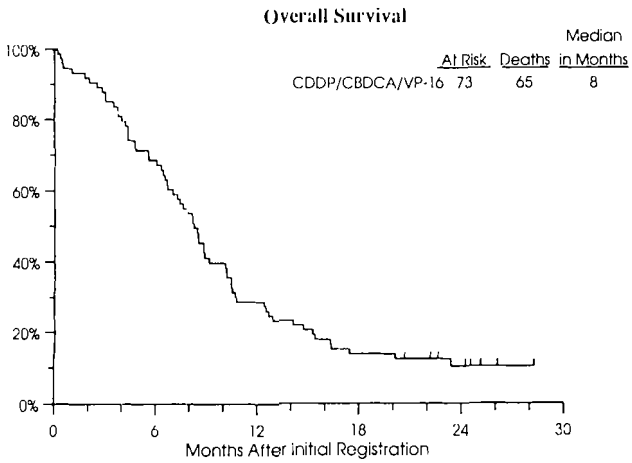

FIGURE 2. Overall survival of patients in study.

TABLE 2
Maximum Toxicities (73 patients)

	Grade (%)		
	3	4	Total
Granulocytopenia	18	48	66
Thrombocytopenia	27	29	56
Leukopenia	36	18	54
Nausea/vomiting	32	4	36
Anemia	18	4	22

(5%). Five patients had responses that could not be confirmed with appropriate and timely follow-up testing (7%) and in 9 patients response assessment was inadequate (12%). The median progression free survival time was 4 months and the median survival time was 8 months. Median survival time was 10 months for ECOG performance status 0,1 patients and 4 months for ECOG performance status 2 patients. Progression free survival and overall survival are shown in Figures 1 and 2 respectively.

Table 2 summarizes the Grade 3 and 4 toxicities. Toxicity was moderately severe. The number of patients with a maximum graded toxicity 1 and 2 was 10 (13%); 23 patients had maximum Grade 3 toxicity (31%); 36 patients had a maximum Grade 4 toxicity (48%), and 6 patients died (8%): 3 patients due to respiratory infection, 2 due to pulmonary edema (1 associated with renal failure), and 1 due to bowel obstruction. All deaths but one (postobstructive pneumonia) were felt to be treatment-related. Grade 3 or 4 hematologic toxicity was most common: leukopenia in 39 patients (52%), granulocytopenia in 48 patients (64%), anemia in 16 patients (21%), and thrombocytopenia in 40 patients (53%). Febrile neutropenia was noted in 15 patients (42%) with Grade 4 granulocytopenia. Seven patients (9%) experienced nephrotoxicity (one patient with Grade 4).

DISCUSSION

Chemotherapy dose intensification is a potentially important strategy in cancer treatment.[25] For cisplatin, experimental studies have demonstrated a steep dose-response relationship in vitro in a variety of tumor types.[17,18,26,27] A variety of strategies have been used to attempt dose escalation clinically using either cisplatin or carboplatin alone.[17,18,28] Recently, there has been an interest in therapy combining cisplatin and carboplatin as a means of escalating the effective dose of platinum-based chemotherapy.[19–21] Several groups have investigated the administration of cisplatin and carboplatin, showing thrombocytopenia and leukopenia to be the dose-limiting toxicity. Nausea and vomiting were similar to cisplatin administration and there were no unusual toxicities with this combination.[19,21]

The activity of both cisplatin and carboplatin are enhanced when combined with noncross-resistant chemotherapy.[2,29] A pilot Phase I/II study of the combination of cisplatin, carboplatin, and etoposide was performed.[22] Seventeen patients (100%) were eligible with a median performance status of 90% (ECOG 0,1 patient eligible only), with only 3 patients (19%) having had prior weight loss of greater than or equal to 10%. In contrast, in the current study, 27% of patients had a performance status of ECOG 2, a status not permitted in the pilot, 49% had a weight loss greater than or equal to 5 Kg, and 54% had an elevated lactate dehydrogenase (LDH) whereas 47% had some degree of bone involvement, all of which are poor prognostic signs. Nine patients had Stage IIIB and 8 patients had Stage IV disease in contrast to the current study, which had predominantly Stage IV patients (91%). Maximum tolerated dose was established at a carboplatin dose of 225 mg/m^2 on Day 1 followed by 50 mg/m^2 of cisplatin on Days 2 and 3. Etoposide was found to be dose-limiting at 75 mg/m^2 on Days 1, 2, and 3. Sixteen patients were evaluable for response with therapy demonstrating a partial response in 9 patients of 56% (95% CI, 30–80%). This study demonstrated that cisplatin, carboplatin, and etoposide combination chemotherapy had activity in patients with advanced nonsmall cell lung carcinoma with dose-limiting hematologic toxicity. Granulocytopenia and thrombocytopenia were Grade 3 and 4 in 76% and 11%, respectively.

The current study was initiated to evaluate this regimen in a cooperative group setting. The confirmed response rate of 24% is not markedly superior to that of

other comparable cisplatin- or carboplatin-containing combination regimens.[30,31] The median progression free and median survival times of 4 months and 8 months, respectively, were also not substantially better than comparable studies using either agent alone or in similar combinations.[30,31] However, toxicity was moderately severe, with only eight patients suffering Grade 2 or lower toxicity as maximal toxicity and these toxicities were mainly hematopoietic. The Calvert dosing system[32] was not used in either the pilot or the current trial, which may account in part for the frequency of hematopoietic toxicity. These trials were being performed just as the Calvert dosing system was being published. Granulocytopenia and thrombocytopenia were Grade 4 in 47% and 27% of patients, respectively. There were six deaths due to a variety of causes, including ileus, pulmonary edema, renal failure, and respiratory infection. We concluded that there is no clear evidence of improved response rate, progression free survival, or overall survival using this regimen, but that toxicity is higher than that described for other trials using cisplatin and etoposide or carboplatin and etoposide combination therapy. The higher response rate in the pilot study may be related in part to patient selection factors, including a better overall performance status, more Stage IIIB patients, and fewer patients with weight loss, bone involvement, and an elevated LDH.

A Phase III trial that compared low dose cisplatin (60 mg/m^2) with high dose cisplatin (120 mg/m^2) both combined with vindesine suggested that although the response rates for the 2 treatment groups were comparable (46% vs. 40%), the high dose regimen was superior to the low dose regimen in median duration of response (12 months vs. 5.5 months) and in median survival (21.7 months vs. 10 months) for responding patients.[30] However, this finding was not confirmed in a subsequent randomized trial evaluating cisplatin-etoposide combinations.[31]

Other clinical trials in nonsmall cell lung cancer have also failed to demonstrate an advantage of platinum dose intensity over standard dose platinum. Gandara et al.[23] evaluated cisplatin dose intensity in metastatic nonsmall cell lung carcinoma in a Phase III study comparing standard dose cisplatin with high dose cisplatin and high dose cisplatin plus mitomycin-C. Confirmed, complete, or partial responses were 12%, 14%, and 27%, respectively. Complete responses were uncommon and were observed only in the high dose cisplatin arms. Progressive disease occurred more frequently in the standard dose cisplatin arms. Progressive disease occurred more frequently in the standard dose cisplatin arm compared with the high dose cisplatin or high dose cisplatin plus mitomycin-C arms (57%, 38%, and 34%, respectively; $P < 0.05$). However, there were no significant differences in median survival time between the three treatment arms, although the delivered dose intensity for cisplatin was significantly greater in the high dose arms. The high dose arms resulted in an increased incidence of ototoxicity, emesis, and myelosuppression, but with similar degrees of renal toxicity and neuropathy compared with standard dose cisplatin.

These studies would indicate that the current level of platinum dose intensification that is achievable with cisplatin, carboplatin, or their combination is unlikely to have any clinical impact in the treatment of advanced nonsmall cell lung carcinoma. Although higher response rates may be observed in isolated studies, there appears to be no survival benefit for escalation of cisplatin or carboplatin alone or in combination.

The current study indicates that although the combination of cisplatin with carboplatin and etoposide is feasible, toxicity is high and response rates, progression free survival, and median survival are not appreciably improved. At the time this study was planned, a number of agents subsequently identified as being active in nonsmall cell lung cancer had not been adequately studied in clinical trials. Currently, the platinums are being explored in combination with taxanes and other new drugs such as Gemcitabine, and the promising response rates and survival data with these combinations may make etoposide a less attractive agent to study in nonsmall cell lung cancer. A current three-arm ECOG trial in patients with nonsmall cell lung carcinoma comparing cisplatin and etoposide with cisplatin and paclitaxel at one of two doses has been completed and the results of this trial may impact the use of etoposide and cisplatin as a reference regimen in patients with nonsmall cell lung carcinoma.

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