Cancer Chemother Pharmacol (1991) 29: 71–74

Cancer Chemotherapy and Pharmacology

Carboplatin and vinblastine in advanced non-small-cell lung cancer: a phase II study

D. Doll[1], M. Goutsou[2], S. Graziano[3], J. Ellerton[4], J. Bitran[5], C. Modeas[6], J. Herndon[7], M. Perry[8], and M. Green[9]

[1] Department of Medicine, University of Missouri, Columbia, MO
[2] Department of Biostatistics, Harvard School of Public Health, Boston, MA
[3] Department of Medicine, SUNY Health Science Center, Syracuse, NY
[4] Southern Nevada Cancer Research Foundation, CCOP, Las Vegas, NV
[5] Department of Medicine, University of Chicago, Chicago, IL
[6] Frontier Science Technology and Research Foundation, Amhurst, NY
[7] Department of Biostatistics, Duke University Medical Center Durham, North Carolina
[8] Department of Medicine, University of Missouri, Columbia, MO
[9] Department of Medicine and Cancer Center, University of California at San Diego, San Diego, CA

Received 28 January 1991/Accepted 2 July 1991

Summary. Between July 2, 1987, and August 21, 1987, Cancer and Leukemia Group B (CALGB) conducted a phase II evaluation of carboplatin (CBDCA) and vinblastine (VBL) in advanced non-small-cell lung cancer. Of the 58 patients who entered the study, 55 were eligible and produced follow-up data. Chemotherapy, which was carried out in 28-day cycles, consisted of 4 mg/m^2 VBL given on days 1 and 3 and 125 mg/m^2 CBDCA given on days 1–3. Partial responses were observed in 10 cases (18%), and 1 patient (2%) exhibited regression of evaluable disease. No complete responses were achieved. The overall objective response rate was 20%. The median survival was 6.1 months, and the median time to treatment failure was 3.3 months. Life-threatening (grade 4) toxicity was mainly leukopenia (20%), followed by anemia (7%), infection (4%), thrombocytopenia (2%), fever (2%), nausea and vomiting (2%), and weight loss (2%). There were two deaths due to infection. The results of this study demonstrate that the combination CBDCA/VBL is active in advanced NSCLC; however, whether this combination is more active than either CBDCA or VBL alone is unknown.

Introduction

Despite treatment, the prognosis for patients presenting with advanced non-small-cell lung cancer (NSCLC) is poor. Although cisplatin-containing chemotherapy regimens have become the mainstay of clinical trials in this disease [3], there is little evidence that such chemotherapy significantly prolongs survival or improves the quality of life in patients with NSCLC [1, 2, 5, 9, 12–14]. Cisplatin therapy is limited by nausea and vomiting, ototoxicity, peripheral neuropathy, and impaired renal function [1, 2, 5, 9, 12–14]. Since palliation and quality of life are therapeutic goals in advanced NSCLC, studies evaluating agents that produce similar activity but less toxicity than cisplatin have been initiated.

Carboplatin (CBDCA), a platinum analogue, is less neurotoxic, emetogenic, ototoxic, neurotoxic, and nephrotoxic than cisplatin [4]. Thus, CBDCA has been introduced into clinical trials and has shown activity against a variety of tumors, including lung cancer [4]. In a prior investigation by Cancer and Leukemia Group B (CALGB study 8431), single-agent CBDCA produced a response rate of 16% in patients presenting with extensive NSCLC [10]. Other studies have confirmed single-agent activity for CBDCA in similar NSCLC patients [2, 6]. In a CALGB phase I trial (study 8631) of daily ×3 doses of etoposide (VP-16) and CBDCA in advanced, previously untreated small-cell lung cancer, the maximal tolerated dose of VP-16 was 200 mg/m^2 daily ×3 and that of CBDA was 125 mg/m^2 daily ×3 as repeated every 4 weeks. A pilot study of vinblastine (VBL) and CBDCA carried out by the McGill group in untreated NSCLC patients who had not undergone prior chemotherapy demonstrated that 4 mg/m^2 VBL given i.v. on days 1 and 3 along with 125 mg/m^2 CBDCA given i.v. on days 1–3 at intervals of 4 weeks resulted in an acceptable level of acute toxicity. Hence, the present trial was undertaken to define the activity and toxicity of the combination of CBDCA and VBL in patients presenting with advanced NSCLC.

Patients and methods

Patients presenting with histologically documented metastatic lung carcinoma of stage III (T_4 by virtue of a cytologically positive pleural effusion with any N and MO) or IV (M1 with any T or N or recurrent disease in the chest following radiotherapy and/or surgery) were considered to be eligible for the present study if they exhibited measurable or evaluable disease, a CALGB performance status of 0–2, no history of chemotherapy, blood urea nitrogen (BUN) and bilirubin levels of <1.5 times the normal values; creatinine levels of <1.8 mg/dl, a granulocyte count of >1800/mm^3, a hemoglobin value of >10 g/dl, and a platelet count of >100,000/mm^3. Other eligibility requirements included no prior or concomitant malignancy, no other serious medical or psychiatric illness, and

Offprint requests to: D. C. Doll, Department of Medicine, University of Missouri, Columbia, MO 65201, USA

Table 1. Patients' characteristics

		Patients	
		(*n*)	(%)
Sex:			
	M	36	(65)
	F	19	(35)
Performance status:			
	0	16	(29)
	1	25	(45)
	2	14	(25)
Previous radiotherapy:			
	No	32	(58)
	Yes	23	(42)
Histology:			
	Adenomatous	22	(40)
	Squamous-cell	15	(27)
	Large-cell	13	(24)
	Undifferentiated non-small-cell	5	(9)
Age:			
	<60 years	25	(45)
	60+ years	30	(55)
	(median, 60 years; range, 37–83 years)		
Disease assessment:			
	Measurable	50	(91)
	Evaluable	5	(9)

a life expectancy of >2 months. Written informed consent was obtained from all patients, and the protocol was approved by th institutional review board of all participating institutions.

Pretreatment evaluation included a complete blood count, a chemistry profile, urinalysis, determination of creatinine clearance, a chest radiograph, a computed tomography (CT) scan of the chest and upper abdomen, and an electrocardiogram. A physical examination and hematology and chemistry profiles were performed before each course of chemotherapy. If findings were abnormal, a chest X-ray was obtained after two cycles of treatment and then every other cycle. If the CT scan initially appeared abnormal it was repeated after two courses of therapy, and subsequently scans were obtained at the discretion of the investigator.

Chemotherapy was given in 28-day cycles starting on day 1, whereby 4 mg/m^2 VBL was given by i.v. bolus on days 1 and 3 and 125 mg/m^2 CBDCA was given i.v. on days 1–3 over 30 min in 100 ml 5% dextrose water. Antiemetics were used at the discretion of the treating physicians. The first cycle of chemotherapy was always given at the full dose. Dose modifications for subsequent cycles were based on the occurrence of hematologic, renal, or neurologic toxicity on the day of treatment or between cycles of therapy. Treatment was discontinued if tinnitus, high-frequency hearing loss, or allergic reactions developed. In patients exhibiting an objective response or stable disease, therapy was continued until there was evidence of disease progression. Treatment was continued for a minimum of two cycles unless rapid disease progression was documented.

A complete response was defined as the complete disappearance of all measurable or evaluable disease for a minimum of 30 days. A partial response was defined as a decrease of $\geq$50% in the size of all measurable lesions for at least 30 days. Regression (evaluable disease only) was defined as a decrease in tumor size for at least 8 weeks as assessed by two independent investigators. Stable disease was defined as a reduction of <50% and an increase of <25% in the sum of the perpendicular diameters of all measurable lesions or no change in tumor size (evaluable disease). Progression was defined as an objective increase of >25% in the size of the lesion or the appearance of any new lesion.

Table 2. Response rate

	Patients	
	(*n*)	(%)
Partial response	10	(18)
Regression	1	(2)
Stable disease	18	(33)
Progression	21	(38)
Early death, not disease-related	3	(5)
Unevaluable	2	(4)

Survival was calculated from the date of study entry until the date of death due to any cause or until the date of the last follow-up examination. Time to failure was measured from the study entry until the date of relapse or death for responders and from the date of study entry until progression or death for nonresponders. Confidence intervals (CI) for response frequencies were calculated using exact binomial distribution. Differences in response rates were assessed using Fisher's exact test [11]. Unadjusted median time events were estimated from Kaplan-Meier curves, and differences in time distributions were evaluated by the log-rank test [7, 8].

Results

Between July 2, 1987, and August 21, 1987, a total of 58 patients were enrolled in the present trial. Three patients were excluded: one did not have extensive disease and two were not started on treatment because of infection. Characteristics of the 55 eligible patients are shown in Table 1.

Table 2 depicts the response data. No complete responses were observed. The overall response rate (partial responses and regression) was 20% (95% CI, 10%–33%). Five patients were unevaluable for response because of early death (three cases) or inadequate treatment (two cases); however, all five subjects were included in the overall response rate. Of the three early deaths, one patient expired due to congestive heart failure, one succumbed to aspiration pneumonia, and one died of sepsis. Death was not attributable to the disease process itself in any of these subjects. There was no statistically significant difference in response rates when patients exhibiting a good performance status (0,1) were compared with those showing a performance status of 2.

Median survival was estimated at 6.1 months (Fig. 1); the estimated 6-month survival for all patients was 54% (SE = 7%). Performance status was significantly associated with survival (log-rank $P = 0.036$), with patients whose performance status was 2 exhibiting a shorter survival. The median time to failure was established at 4.4, 3.3, and 1.9 months for subjects showing a performance status of 0, 1, and 2, respectively; performance status was not significantly associated with failure-free survival ($P = 0.3123$).

Toxicity data are shown in Table 3. Toxicities predominantly involved leukopenia, thrombocytopenia, anemia, nausea and vomiting, weight loss, and alopecia. There were two deaths due to granulocytopenic infection. One patient developed life-threatening thrombocytopenia and required platelet transfusions. All subjects received full-

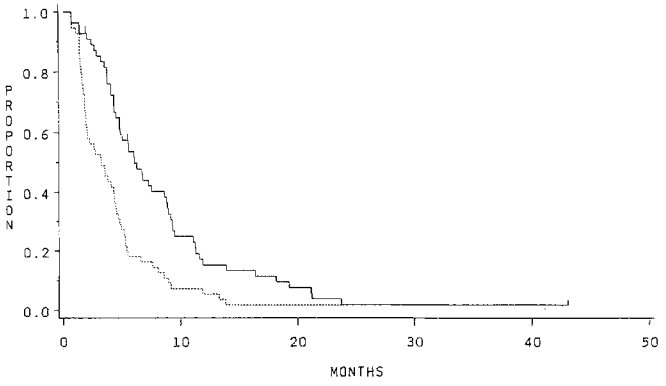

Fig. 1. Survival of NSCLC patients and time to failure during treatment with CBDCA and VBL.

	Strata	NFailures	(%)	Median	
(———)	Survival	55	52	95	6.10
(– – – –)	TTF	55	54	98	3.25
	Total	110	106	96	

dose chemotherapy for cycle 1; 12 patients (22%) required subsequent dose modifications.

Discussion

Cisplatin combination regimens are often used in NSCLC. Trials using vinca alkaloids or etoposide in combination with cisplatin have produced an overall response ranging from 12% to 69% [3]. However, severe nausea and vomiting occur frequently on cisplatin treatment, and normal renal function and time-consuming hydration are necessary for the prevention of severe nephrotoxicity.

In our phase II study using CBDCA/VBL, an overall response rate of 20% was observed. As compared with our previous phase II data for CBDCA alone [10], the addition of VBL resulted in only a slight increase in remission rates (20% vs 16%). In the previous trial, CBDCA was given at a dose of 400 mg/m^2 every 28 days [10]. The Eastern Cooperative Oncology Group obtained a response rate of 9% using CBDCA in patients presenting with NSCLC; CBDCA was associated with a longer median survival and failure-free survival as compared with cisplatin combinations [2]. A randomized trial comparing CBDCA with CBDCA plus etoposide in previously untreated inoperable NSCLC resulted in a response rate of 20% for CBDCA and 26.7% for the combination [6]. In that study, 66.7% of patients displaying limited disease responded to CBDCA/etoposide as compared with 16.2% of those exhibiting extensive disease.

Myelosuppression is the dose-limiting toxicity of CBDCA. Life-threatening leukopenia developed in 20% of patients in our study, and there were two deaths due to infection. Gatzemeier et al. [6] reported that myelosuppressive toxicity during combination chemotherapy was substantially greater than that observed during treatment with CBDCA alone. Although the optimal CBDCA dose in combination chemotherapy is not known, perhaps a dose of 300 mg/m^2 $\times 1$ or 100 mg/m^2 $\times 3$ might ameliorate severe leukopenia in drug regimens that incorporate additional myelotoxic agents.

The median survival was 6.1 months, and patients showing a performance status of 0 or 1 lived significantly longer than those exhibiting a performance status of 2. The median survival of CBDCA/etoposide-treated patients reported by Gatzemeier et al. [6] was 4.5 months, and performance status was not a statistically significant factor for survival.

The results of the present phase II trial demonstrate that CBDCA/VBL is active in patients presenting with advanced NSCLC. However, as toxicity was significant, we do not recommend that this regimen be used as standard therapy in such patients. Whether CBDCA/VBL or other CBDCA combinations are better than carboplatin alone is unknown. Since the dose-limiting toxicity of the latter is primarily myelosuppression, trials using higher doses of CBDCA in association with colony-stimulating factors should be considered.

Acknowledgement. We are grateful to Ms. S. Brown for her expert secretarial assistance.

Table 3. Frequency and grade of toxicities[a]

Type of toxicity	None		Mild		Moderate		Severe		Life-threatening		Lethal	
	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)
Leukopenia	9	(16%)	8	(15%)	11	(20%)	16	(29%)	11	(20%)	0	(0)
Thrombocytopenia	25	(45%)	10	(18%)	5	(9%)	14	(25%)	1	(2%)	0	(0)
Anemia	4	(7%)	8	(15%)	24	(44%)	15	(27%)	4	(7%)	0	(0)
Fever	30	(56%)	6	(11%)	8	(15%)	9	(17%)	1	(2%)	0	(0)
Infection	37	(67%)	3	(5%)	5	(9%)	6	(11%)	2	(4%)	2	(4%)
Hepatic	35	(64%)	12	(22%)	8	(15%)	0	(0)	0	(0)	0	(0)
Renal	33	(60%)	14	(25%)	6	(11%)	2	(4%)	0	(0)	0	(0)
Nausea and vomiting	18	(33%)	12	(22%)	11	(20%)	13	(24%)	1	(2%)	0	(0)
Weight loss	19	(35%)	1	(2%)	30	(56%)	3	(6%)	1	(2%)	0	(0)
Neurotoxicity (CNS)	41	(75%)	6	(11%)	8	(15%)	0	(0)	0	(0)	0	(0)
Neurotoxicity (PNS)	40	(73%)	7	(13%)	8	(15%)	0	(0)	0	(0)	0	(0)
Alopecia	31	(56%)	5	(9%)	11	(20%)	8	(15%)	0	(0)	0	(0)

[a] Common toxicity criteria
PNS, Peripheral nervous system

Appendix

The present study was conducted by Cancer and Leukemia Group B and was supported by Public Health Service Grants from the National Cancer Institute, National Institutes of Health, and the Department of Human Services and by a grant from the T. J. Martell Foundation. The following members participated in the study:

SUNY-Health Science Center, Syracuse, New York, Arlan Gottlieb (CA-21 060)

University of California at San Diego, San Diego, California, Mark Green (CA-11 789)

McGill Cancer Center, Montreal, Canada, J. L. Hutchinson (CA-31 809)

New York Hospital-Cornell Medical Center, New York, New York, Richard T. Silver (CA-07 968)

Rhode Island Hospital, Providence, Rhode Island, Louis Leone (CA-08 025)

Duke University Medical Center, Durham, North Carolina, Robert C. Bast

Long Island Jewish Medical Center, New Hyde Park, New York, Kandi Rai (CA-11 028)

Massachusetts General Hospital, Boston, Massachusetts, Robert Carey (CA-12 449)

University of Cincinnati College of Medicine, Cincinnati, Ohio, Orlando Martelo

Central Massachusetts Oncology Group, Worcester, Massachusetts, Mary Costanza (CA-37 135)

Dartmouth-Hitchcock Medical Center, Hanover, New Hampshire, Gibbons Cornwell (CA-04 326)

University of Iowa, Iowa City, Iowa, Gerald Clamon

Washington University Medical Center, St. Louis, Missouri, Alan P. Lyss

Maimonides Hospital, New York, New York, Sameer Rafla (CA-25 119)

University of Alabama, Birmingham, Alabama, George Omura

University of Chicago, Chicago, Illinois, Harvey Golomb

University of Missouri, Columbia, Missouri, Michael C. Perry (CA-12 046)

University of Minnesota, Minneapolis, Minnesota, Bruce Peterson (CA-16 450)

University of Maryland Cancer Center, Baltimore, Maryland, Joseph Aisner (CA-31 983)

Mount Sinai School of Medicine, New York, New York, James F. Holland (CA-04 457)

Walter Reed Army Medical Center, Washington, D. C., Raymond Weiss (CA-26 806)

Harvard School of Public Health, Boston, Massachusetts, James R. Anderson (CA-33 601)

References

1. Blumenreich MS, Woodcock TM, Gentile PS, Barnes GV, Vose B, Sherrill EJ, Richman SP, Epremian BE, Kubota TT, Allegra JC (1987) High-dose cisplatin and vinblastine infusion with or without radiation therapy in patients with advanced non-small cell lung cancer. J Clin Oncol 5: 1725–1730
2. Bonomi PD, Finkelstein DM, Ruckdeschel JC, Blum RH, Green MD, Mason B, Hahn R, Tormey DC, Harris J, Comis R, Glick J (1989) Combination chemotherapy versus single agents followed by combination chemotherapy in stage IV non-small cell lung cancer: a study of the Eastern Cooperative Oncology Group. J Clin Oncol 7: 1602–1613
3. Bunn PA Jr (1989) The expanding role of cisplatin in the treatment of non-small cell lung cancer. Semin Oncol 16 [Suppl]: 10–21
4. Bunn PA Jr (1989) Review of therapeutic trials of carboplatin in lung cancer. Semin Oncol 16: [Suppl]: 27–33
5. Ganz PA, Figlin RA, Haskell CM, LaSoto N, Sian J (1989) Supportive care versus supportive care and combination chemotherapy in metastatic non-small lung cancer: does chemotherapy make a difference? Cancer 63: 1271–1278
6. Gatzemeier U, Heckmayr M, Neuhauss R, Hossfeld D, Achterrath W, Lenaz L (1990) Phase II studies with carboplatin in non-small cell lung cancer. Semin Oncol 17 [Suppl]: 25–31
7. Kalbfleisch JD, Prentice RL (1980) The statistical analysis of failure time data. (Wiley series in probability and mathematical statistics) John Wiley and Sons, New York
8. Kaplan EL, Meier RL (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53: 457–481
9. Klastersky J, Sculier JP, Bureau G, Libert P, Ravez P, Vandermoten G, Thinlaux V, Lecomte J, Cordier R, Dabouis G, Brohée D, Thèmelin L, Mommen P (1989) Cisplatin versus cisplatin plus etoposide in the treatment of advanced non-small cell lung cancer. J Clin Oncol 7: 1087–1092
10. Kreisman H, Ginsberg S, Propert KJ, Richards F, Graziano S, Green M (1987) Carboplatin or iproplatin in advanced non-small cell lung cancer: a cancer and Leukemia Group B study. Cancer Treat Rep 71: 1049–1052
11. Mehta CR, Patel NR (1983) A network algorithm for the exact treatment of Fisher's exact test in RxC contingency tables. J Am Stat Assoc 78: 382, 427–434
12. Rapp E, Pater JL, Willan A, Cormièr Y, Murray N, Evans WK, Hodson DI, Clark DA, Feld R, Arnold AM, Ayoub VI, Wilson KS, Latreille V, Wierzbicki RF, Hill DP (1988) Chemotherapy can prolong survival in patients with advanced non-small cell lung cancer – report of a Canadian multicenter randomized trial. J Clin Oncol 6: 633–641
13. Rosell R, Abad-Esteve A, Moreno I, Barnadas A, Carles J, Fernandez C, Ribelles N, Culubret M (1990) A randomized study of two vindesine plus cisplatin-containing regimens with the addition of mitomycin C or ifosfamide in patients with advanced non-small cell lung cancer. Cancer 65: 1692–1699
14. Williams CJ, Woods R, Levi J, Page J (1988) Chemotherapy for non-small cell lung cancer: a randomized trial of cisplatin/vindesine vs no chemotherapy. Semin Oncol 15 [Suppl]: 58–61