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High-dose cisplatin and mitomycin C in advanced non-small cell lung cancer: a phase II study of the Northern California Oncology Group*

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Summary. To investigate chemotherapeutic dose intensity in advanced non-small-cell lung cancer (NSCLC), we evaluated a pharmacokinetically designed schedule of high-dose cisplatin (200 mg/m^2 per 28-day cycle) plus mitomycin C. Between March 1987 and March 1989, 62 patients were registered for a phase II study of the Northern California Oncology Group (NCOG). The treatment schedule consisted of cisplatin in hypertonic saline given on a divided days 1 and 8 schedule (100 mg/m^2 on each day) plus mitomycin C given at a dose of 8 mg/m^2 on day 1 of each cycle. In 61 patients evaluable for response analysis, the overall response rate was 39% (24/61), with a complete response being achieved in 6% (4/61) of cases and a partial response, in 33% (20/61). The response according to reviewed histologic subtype included squamous, 53% of patients (10/19); large cell, 31% (4/13); and adenocarcinoma, 34% (10/29). The median survival for all patients was 29.3 weeks. The mean cisplatin and mitomycin C delivered dose intensities in this study were 45 mg/m^2 per week (90% of the projected dose) and 1.5 mg/m^2 per week (75%). The toxicity of this combination regimen in the 62 enrolled patients was significant but manageable. Leukopenia (WBC, <1,000/mm^3) and thrombocytopenia (platelets, <25,000/mm^3) occurred in 3% and 8% of patients treated, respectively. Dose-limiting renal toxicity and clinically significant ototoxicity developed in 8 patients each (13%), and a peripheral sensory neuropathy was observed in 17 cases (27%). Whether this type of dose-intensive therapy results in an improved therapeutic index in NSCLC is currently being evaluated in a randomized comparative trial versus standard-dose cisplatin therapy.

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Introduction

Although metastatic non-small-cell lung cancer (NSCLC) has long been considered to be poorly responsive to chemotherapy, there are now at least five chemotherapeutic agents that have demonstrated reproducible antitumor activity in this disease. These include cisplatin and its analogue carboplatin, the investigational agent vindesine, ifosfamide, and mitomycin C. Of the single agents currently available, cisplatin may have the greatest degree of activity, with cumulative response rates of 14% and 19% being reported in two reviews [10, 24]. Even for cisplatin, however, the reported single-agent activity has been quite variable, ranging from 0 to 33% [2, 4, 5, 19, 25].

The results of a Canadian multicenter trial comparing two different chemotherapy regimens with best supportive care confirm that cisplatin-based therapy offers a modest improvement in survival in NSCLC [22]. Whether cisplatin-containing combination therapy is superior to cisplatin or carboplatin alone is debatable. In a recent study by Klastersky et al. [14], who compared cisplatin alone (120 mg/m^2) with cisplatin plus etoposide, neither the response rates (19% vs 26%) nor the median survival values (26 vs 22 weeks) were significantly different between the two treatment arms. A five-arm study of the Eastern Cooperative Oncology Group (ECOG 1583) evaluated three cisplatin-containing combinations and the single agents carboplatin and iproplatin. Although the carboplatin arm produced only a 9% response rate, the median survival of 31.7 weeks was superior to that of any of the combinations as well as that of the iproplatin arm [3].

The optimal dose of cisplatin in the treatment of many malignancies remains undefined [6]. A review of early trials of single-agent cisplatin in NSCLC shows a positive dose-response relationship as the projected dose intensity increases from 18–20 to 25–37.5 mg/m^2 per week [7]. However, the actual delivered dose is not described in any of these reports. In a recently completed phase II trial of the Northern California Oncology Group (NCOG), the response rate for single-agent high-dose cisplatin given at a projected dose intensity of 50 mg/m^2 per week (200 mg/m^2

Table 1. Patient characteristics

Number of patients registered		62
Age in years	Mean	58
	Range	(39–69)
Sex:	M	38
	F	24
Karnofsky performance status:	70– 80	32
	90–100	30
Histology:	Adenocarcinoma	30
	Squamous	19
	Large cell	13
Stage:	IIIB	12
	IV	50
Prior radiotherapy:	yes	16
	no	46

per 28-day cycle) was 36%, with a complete response being reported in 8% of cases. The median survival in 76 evaluable patients was 37 weeks [7]. The actual delivered dose intensity of cisplatin was 47 mg/m^2 per week, or 94% of the projected dose. These results are superior to those previously reported for single-agent cisplatin in NSCLC and appear to be comparable with those obtained for many combination chemotherapy regimens in this disease. The data support the concept that the cisplatin dose may be important in determinations of chemotherapeutic response and survival in NSCLC.

Of other chemotherapeutic agents with activity against NSCLC that could be tested in combination with high-dose cisplatin, mitomycin C appears to be a good candidate. Cisplatin and mitomycin C demonstrate additive, if not synergistic, cytotoxicity in vitro and these two agents are clinically characterized by nonoverlapping toxicity patterns [20, 23]. In previous trials in NSCLC, the cumulative response rate for mitomycin C has been reported to be 18% in a group of previously untreated patients [15]. The present report describes our experience in an NCOG phase II trial investigating the efficacy and toxicity of high-dose cisplatin plus mitomycin C in advanced NSCLC, along with an analysis of the delivered dose intensity in patients receiving this regimen.

Patients and methods

Patient selection. Criteria for study entry consisted of histologically or cytologically demonstrated advanced NSCLC (stage IIIB or IV according to the International Staging System) that had not been previously treated with chemotherapy [16]. Recurrence in the lung following prior surgery or radiotherapy was included as metastatic disease. All patients had measurable disease, a Karnofsky performance status (KPS) of >60%, a serum creatinine value of <1.5 mg% and creatinine clearance of ≥65 ml/min, a WBC count of ≥4,000/mm^3, and a platelet count of ≥150,000/mm^3. Patients with known brain metastases were excluded from the study. All patients gave informed, written consent to participate in this cooperative group study.

Patient characteristics. From March 1987 through March 1989, 62 patients with advanced NSCLC were entered in this study from nine different member institutions of the NCOG. Patient characteristics at the time of study entry are summarized in Table 1. The mean age for all patients was 58 years (range, 39–69 years), and the study population consisted of 38 men and 24 women. The median KPS at study entry was 80% (range, 70%–100%). Pathologic material from all patients entered in this trial underwent central review by a single pathologist. Histologic subclassification showed 19 squamous-cell carcinomas, 30 adenocarcinomas, and 13 large-cell carcinomas. In all, 12 patients had stage IIIB cancer and 50 subjects had stage IV disease.

Treatment schedule. Cisplatin total dose/cycle (200 mg/m^2), was given in two doses of 100 mg/m^2 each on days 1 and 8 of each 28-day cycle. Cisplatin was reconstituted and infused in 250 ml 3% saline over 3 h. Patients were prehydrated with normal saline at 150–250 ml/h plus potassium and magnesium supplementation for 12 h prior to treatment. During the 3-h cisplatin infusion, hydration was continued with normal saline at 250 ml/h. Following the completion of drug infusion, a minimum of 500 ml normal saline was given additionally. In patients who could not maintain a high level of posttreatment oral intake, additional intravenous hydration was carried out. Treatment was preceded by parenteral antiemetics. Mitomycin C (8 mg/m^2) was given as a slow intravenous bolus on day 1 of each 28-day cycle.

Modification of the drug schedule. Prior to day 1 of each cycle, determinations of serum creatinine, creatinine clearance (24-h collection), WBC count, platelet count, and electrolytes including serum magnesium were carried out. Patients received drug therapy only when the following criteria were met: creatinine clearance of ≥50 ml/min, WBC count of >3,500/mm^3, and platelet count of >125,000/mm^3. If these criteria were not met, day-1 therapy was withheld for 1 week and laboratory studies were repeated. Reduction of the cisplatin dose was not permitted in this study. Therefore, each dose always amounted to 100 mg/m^2. Prior to each day-8 drug treatment, only the serum creatinine value was obtained. Cisplatin was given on day 8 if the increase in serum creatinine was ≤0.5 mg% and the serum creatinine value was ≤1.5 mg%. For any increase in creatinine of >0.5 mg%, or if the serum creatinine level was >1.5 mg%, the creatinine clearance was determined, with requirements for treatment as described above. The dose of mitomycin C was reduced by 50% if leukopenia (WBC, <1,000/mm^3) or thrombocytopenia (platelets, <25,000/mm^3) had been documented during the previous cycle.

Response and toxicity criteria. Standard cooperative group criteria (NCOG) were used, including clinical grading of otoxicity and peripheral neuropathy [8]. Patients with either >grade III ototoxicity or neuropathy or persistent creatinine clearance of <50 ml/min were removed from the study. Patients with stable disease after two cycles of therapy were considered to be nonresponders and were also removed from the study.

Statistical analysis. Differences in response rates between groups were evaluated with univariate analysis using the chi-square test [1]. Survival curves were plotted using the method of Kaplan and Meier, and comparisons of survival distribution were made by the nonparametric log-rank test [13, 21].

Results

A total of 62 patients from 9 NCOG institutions were registered for this study. All patients were considered to be evaluable for toxicity analysis; 1 patient was lost to follow-up on day 2 after enrollment and was not considered to be evaluable for response.

Analysis of response

The overall response and the response by reviewed histologic subtype in 61 evaluable patients are shown in Table 2. A complete response was documented in

Table 2. Response of patients to treatment

Detailed overall response	Total number of patients ($n = 61$)
Complete response	4
Partial response of >50%	20
Partial response of <50% or mixed	5
Stable disease	13
Disease progression	15
Response not available	4

Overall response rate	Rate
Complete response rate (CR/evaluable)	4/61 (6%)
Partial response (PR of >50%/evaluable)	20/61 (33%)
Overall objective response (CR+PR of >50%/evaluable)	24/61 (39%)

Response rate by histologic subtype	Squamous	Adenocarcinoma	Large cell
CR rate (CR/evaluable)	3/19 (16%)	1/29 (3%)	0/13 (0)
PR rate (PR of >50%/evaluable)	7/19 (37%)	9/29 (31%)	4/13 (31%)
Overall response (CR+PR of >50%/evaluable)	10/19 (53%)	10/29 (34%)	4/13 (31%)

Table 3. Analysis of response and survival by potential prognostic factors

Prognostic factor	Patients ($n = 61$)	Response[a]	Median survival (weeks)	
Age:				
<60 years	35	12/35 (34%)	26.7	$P = 0.46$
>60 years	26	12/26 (46%)	29.3	
Sex:				
M	38	16/38 (42%)	28.3	$P = 0.62$
F	23	8/23 (35%)	32.6	
KPS:				
70–80	33	12/33 (36%)	24.9	$P = 0.26$
>90	28	12/28 (43%)	34.6	
Histologic type:				
Squamous	19	10/19 (53%)	26.6	
Adenocarcinoma	29	10/29 (34%)	32.6	$P = 0.90$
Large cell	13	4/13 (31%)	28.3	
Stage:				
III	12	7/12 (58%)	36.7	$P = 0.10$
IV	49	17/49 (35%)	27.9	
Prior radiation:				
no	45	20/45 (44%)	31.3	$P = 0.32$
yes	16	4/16 (25%)	19.7	

[a] All comparisons were statistically insignificant according to the chi-square test

4 patients (6%) and a partial response of >50%, in 20 cases (33%), for an overall response rate of 39% (95% confidence intervals, 27%–51%). According to standard Cooperative Group criteria, a partial response of <50% or a mixed response occurred in an additional 5 patients (8%), and these subjects were classified as nonresponders. In all,

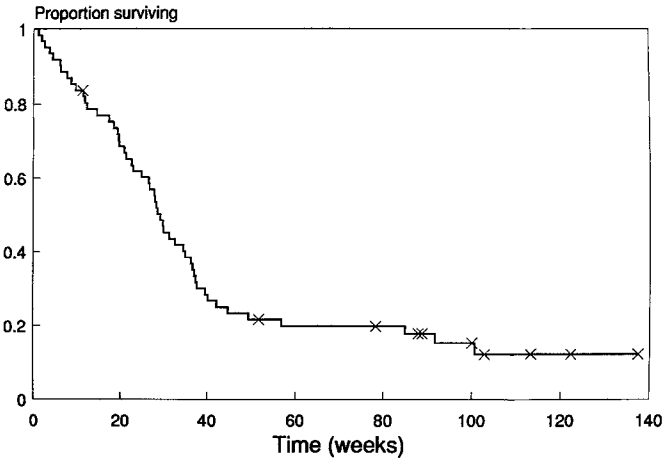

Fig. 1. Survival distribution among 61 patients treated with high-dose cisplatin plus mitomycin C (median, 29.3 weeks)

13 patients were classified as having stable disease, and 15 as having progressive disease during the treatment period. In 4 cases response data were not available, and these patients were considered to be nonresponders. Response by reviewed histologic subtype revealed a response rate of 53% (10/19) in squamous-cell carcinoma, 34% (10/29) in adenocarcinoma, and 31% (4/13) in large-cell carcinoma. In five patients, VP-16 was temporarily substituted for cisplatin during evaluation and treatment of salt-wasting nephropathy or evaluation of ototoxicity [12]; however, in none of these cases could cisplatin subsequently be restarted as defined by protocol criteria. VP-16 did not change the response status in any patient receiving this agent.

Analysis of response and survival by potential prognostic variables is shown in Table 3. There were no statistically significant differences, although trends were present for stage and KPS.

The mean cumulative dose of cisplatin received per patient was 550 mg/m^2 (range, 100–1,200 mg/m^2). Cisplatin dose intensity in this study was determined on a mg/m^2 per week basis during the treatment period, as previously described [11]. Since dose reduction was not permitted, each dose delivered was 100% of the expected dose, and a decrease in dose intensity was related solely to treatment delays. The mean delivered cisplatin dose intensity in this study in all evaluable patients was 45 mg/m^2 per week, or 90% of the projected dose. The mean delivered dose intensity of mitomycin C was 1.5 mg/m^2 per week, or 75% of the projected dose.

The median time to progression and median survival for all patients amounted to 18 and 29.3 weeks, respectively; 20% of patients were 1-year survivors (Fig. 1). The median survival for responders was 39.6 weeks. The median time to progression and median survival according to the three histologic subtypes were not significantly different from one another.

Analysis of toxicity

All 62 patients were considered to be evaluable for toxicity analysis (Table 4). There were no treatment-related deaths

Table 4. Hematologic and nonhematologic toxicities

Toxicities		Grade	Total ($n = 62$)	%
WBC (1,000/mm^3)	3 – 4.4	1	21	(34%)
	2 – 2.9	2	13	(21%)
	1 – 1.9	3	8	(13%)
	<1	4	2	(3%)
Platelets (1,000/mm^3)	99 – 129	1	12	(19%)
	50 – 89	2	8	(13%)
	25 – 49	3	4	(6%)
	<25	4	5	(8%)
Nausea and vomiting		1	19	(31%)
		2	21	(34%)
		3	6	(10%)
		4	1	(2%)
Renal (serum creatinine, mg%)	1.5 – 3	1	19	(31%)
	3.1 – 5	2	1	(2%)
	5.1 – 10	3	0	
	>10	4	0	
Peripheral neuropathy		1	9	(14%)
		2	6	(10%)
		3	2	(3%)
		4	0	
Ototoxicity		1	9	(14%)
		2	8	(13%)
		3	0	
		4	0	

in this study. Leukopenia (WBC, <1,000/mm^3) occurred in 3% (2/62) of cases and thrombocytopenia (platelets, <25,000/mm^3) occurred in 8% (5/62) of patients.

Nausea and vomiting, although common, were severe in only seven patients (12%) and required hospitalization for treatment in only one case. As previously described, the use of hypertonic saline was effective in reducing nephrotoxicity, with only eight patients (13%) developing a serum creatinine value of >2 mg% at any point during therapy; the highest mean serum creatinine level observed was 1.3 mg% (range, 0.5–3.7 mg%). Hypomagnesemia (<1.5 mg%) occurred in 23 patients (37%), and a salt wasting nephropathy manifested by hyponatremia with an inappropriately elevated urinary sodium concentration was observed in 7 subjects (11%) [12].

Neurotoxicity manifesting as a peripheral sensory neuropathy developed in a total of 17 patients (27%), and its onset was often delayed. In 15 patients, this consisted of only mild to moderate paresthesias of the hands and feet; however, in 2 cases, grade III neuropathy consisting of a marked proprioceptive deficit occurred, resulting in a gait disturbance. No patient developed grade IV neuropathy (wheelchair dependence) during this study. Clinically significant ototoxicity occurred in eight patients (13%), but no subject experienced a hearing loss severe enough to require the use of a hearing aid.

Discussion

The present study represents the second in a series of sequential NCOG trials evaluating cisplatin dose intensity in NSCLC. The primary objective of this study was to determine whether mitomycin C, an agent with independent activity and nonoverlapping toxicity, could be effectively combined with a days 1 and 8 high-dose cisplatin regimen previously described by our group [7, 8]. The results demonstrate the feasibility of adding mitomycin C, in a dose schedule commonly used in NSCLC, to this high-dose cisplatin regimen. As would be expected, myelosuppression was more prominent; otherwise, the toxicity pattern of this combination was not substantially different from that of high-dose cisplatin alone. The response rate of 39% and the median survival of 29 weeks are comparable with those reported for many other cisplatin-based regimens. Delivered dose intensity was maintained at a high level, being 45 mg/m^2 per week for cisplatin (90% of the projected value) and 1.5 mg/m^2 per week for mitomycin C (75% of the projected dose). These data for cisplatin are essentially identical to the results we previously obtained for high-dose cisplatin alone, and they show that mitomycin C given at the dose and on the schedule used in this trial does not adversely impact on the delivered dose intensity of cisplatin.

Although chemotherapeutic dose intensity is of considerable interest in a number of tumor types, the actual delivered dose intensity is rarely described in reports of clinical cancer trials [6, 11]. In vitro studies in both clinically sensitive and resistant ovarian and testicular cancer cell lines demonstrate steep dose-response curves, implying that in many cases cisplatin resistance is relative rather than absolute [17]. Clinical studies in cisplatin-sensitive tumors also suggest that the cisplatin dose is important, although this concept remains controversial [6].

In non-small-cell lung cancer (NSCLC), in vitro studies show positive dose-response effects in some but not all cell lines, suggesting considerable heterogeneity in sensitivity to cisplatin [20, 23]. In clinical studies of single-agent cisplatin, response rates in NSCLC have usually correlated with the projected dose intensity. Early studies using projected dose intensities of 18–20 mg/m^2 per week generally resulted in response rates of $\leqslant 10\%$ [4, 7]. By comparison, a study by Vogl et al. [25], who used a very high projected dose intensity of 37.5 mg/m^2 per week, reported a response rate of 33% in metastatic NSCLC [25]. However, since dose delays and dose reduction usually result in a lower delivered dose intensity as compared with projections, information regarding the actual delivered dose (in mg/m^2 per week) would be useful in analyzing the results of these trials.

In the past, attempts to given high-dose regimens of cisplatin, such as the study of Vogl et al. [25], were complicated by an unacceptable level of renal insufficiency. The recent introduction of hypertonic saline and chemoprotective rescue agents to reduce nephrotoxicity has renewed interest in evaluating cisplatin dose intensity [6, 17]. In ovarian cancer and testicular cancer, a 5-day regimen of cisplatin delivering 200 mg/m^2 per 28-day cycle (projected dose intensity, 50 mg/m^2 per week) produced both impressive results and severe toxicity [17, 18]. Based on pharmacokinetic findings of accumulation of potentially toxic ultrafiltrate platinum species following each daily dose of this 5-day regimen, we developed a

divided days 1 and 8 schedule designed to deliver the same dose intensity of cisplatin, but avoiding ultrafiltrate platinum accumulation [8]. A recent NCOG trial evaluating this days 1 and 8 regimen as single-agent therapy in advanced NSCLC demonstrated encouraging response rates and median survival. In addition to reducing nephrotoxicity and peripheral neuropathy, this divided-dose approach also eliminated the severe myelosuppression characterizing 5-day schedules of similar cisplatin dose intensity [7].

The current study demonstrates the feasibility of combining this days 1 and 8 cisplatin regimen with other chemotherapeutic agents that are dose-limited by myelosuppression. A phase III trial by the Southwest Oncology Group now in progress is designed to determine whether increasing dose intensity in NSCLC translates into improved response or survival by directly comparing standard-dose cisplatin with both high-dose cisplatin and the current combination regimen of high-dose cisplatin plus mitomycin C. Apart from its applicability in NSCLC, this cisplatin dose schedule may be of interest in other cisplatin-sensitive tumor types.

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