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Phase II study of carboplatin in patients with nonresected lung cancer

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Summary. A multicenter phase II trial of carboplatin, a new platinum analog of cisplatin, was carried out in bronchogenic carcinoma at 17 institutions throughout Japan. Of 139 patients enrolled in this trial, 10 were excluded from analysis as inevaluable and the remaining 129 were judged to be evaluable for response and toxic effects by the Extramural Review Committee. Patients were treated i.v. with either 300 or 400 mg/m^2 carboplatin every 4 weeks. Responses and toxic effects were assessed at both dose levels. The overall response rate was 17.8% (23/129), with response rates of 28.4% (19/67) for small-cell disease, 7.1% (2/28) for squamous-cell carcinoma, and 6.9% (2/29) for adenocarcinoma. The most frequent toxic effects were thrombocytopenia and leukopenia, with a platelet count of $<7 \times 10^4$ μl recorded in 60 patients (46.5%) and a WBC count of <3,000/μl recorded in 60 cases (46.5%). Vomiting occurred in 28 patients (21.7%). Renal, aural, and neurotoxicities were not seen. Hydration was not required. Carboplatin was demonstrated to be active against lung cancer, especially against small-cell lung cancer.

Introduction

Cisplatin is widely used in the treatment of lung cancer and is recognized to be one of the most active cytotoxic agents for therapy of this disease. However, its utility is often limited by renal impairment, hearing loss, emesis, and peripheral neuropathy. Carboplatin is one of a series of analogs of cisplatin and has been found to be active in most cisplatin-sensitive animal tumors and certain human malignancies, with fewer of cisplatin's undesirable toxic effects such as nephrotoxicity [3, 10]. Phase I trials [1, 5] have demonstrated that carboplatin is less emetogenic and nephrotoxic than cisplatin and that carboplatin may be given without the need for hydration; its dose-limiting toxicity is myelosuppression, especially thrombocytopenia. This report evaluates a multi-institutional phase II trial of carboplatin in patients with nonresected primary lung cancer.

Patients and methods

Between January 1986 and January 1988, 139 patients with histologically or cytologically proven, nonresected primary lung cancer were registered in this trial. All patients had an evaluable or measurable lesion, a life expectancy of ≧3 months a performance status (PS) of ≦3, hemoglobin values of ≧9.5 g/dl, a WBC count of ≧3,500 μl, a platelet count of ≧10×10^4 μl, serum creatinine levels of ≦1.5 mg/dl, GOT·GPT values of <2 times normal, and an age of ≧15 years. In addition, an interval of >4 weeks since any prior chemotherapy or radiation therapy was required. Informed consent was obtained from all patients.

Carboplatin was given at a dose of 300 mg/m^2 in patients with a PS of 2 or 3 and in those who had been heavily pretreated. Patients with a PS of ≦1 and those who had not undergone prior chemotherapy received

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Table 1. Patient characteristics

	Total	300 mg/m^2	400 mg/m^2
Eligible	139	36	103
Evaluable	129	32	97
Sex: men/women	95/34	26/7	69/27
Age: median (range)	71 (33–86) years	72 (41–84) years	71 (33–86) years
Performance status 0–1/2–3	66/63	9/23	57/40
Histology:			
Small-cell	67	17	50
Squamous	28	8	20
Adenocarcinoma	29	5	24
Large-cell	4	1	3
Adenoidocystic	1	1	0
Prior chemotherapy:			
No	78	18	60
Yes	51	14	37
Stage:			
I–II	11	1	10
III	37	7	30
IV	81	24	57

Table 2. Response rates according to cell type

Histology	Patients (n)	CR	PR	MR	NC	PD	CR+PR patients
Small-cell	67	0	19	3	27	18	19/67 (28.4%)
Squamous	28	0	2	7	15	4	2/28 (7.1%)
Adenocarcinoma	29	0	2	1	20	6	2/29 (6.9%)
Large-cell	4	0	0	0	4	0	0/4 (0)
Adenoidocystic	1	0	0	0	0	1	0/1 (0)
Totals	129	0	23	11	66	29	23/129 (17.8%)

Table 3. Response rates acccording to dose

	Dose (mg/m^2)	Patients(n)	CR	PR	MR	NC	PD	CR+PR patients	Chi-square-test
Overall	300	33	0	2	3	16	12	2/33 (6.1%)	$P<0.1$
	400	96	0	21	8	50	17	21/96 (21.9%)	
Small-cell	300	17	0	2	1	7	7	2/17 (11.8%)	
	400	50	0	17	2	20	11	17/50 (34.0%)	
Non-small-cell	300	15	0	0	2	8	5	0/15 (0)	
	400	47	0	4	6	31	6	4/47 (8.5%)	

Table 4. Response rates according to disease stage

	Patients (n)	CR	PR	MR	NC	PD	CR+PR patients
Small-cell:							
Stage I/II	4	0	2	0	2	0	2/4 (50.0%)
III	17	0	7	1	8	1	7/17 (41.2%)
IV	46	0	10	2	17	17	10/46 (21.7%)
Non-small-cell:							
Stage I/II	7	0	1	1	5	0	1/7 (14.3%)
III	20	0	3	3	12	2	3/20 (15.0%)
IV	35	0	0	4	22	9	0/35 (0%)

400 mg/m^2. Carboplatin was given as an i.v. infusion over 1 h with 500 ml 5% dextrose, and drug administration was repeated every 4 weeks.

The patients were evaluated for response and toxic effects by the Extramural Review Committee according to the criteria of the Japan Society for Cancer Therapy, which were modified from WHO criteria. A complete response (CR) was defined as the total disappearance of all clinical evidence of disease for at least 4 weeks. A partial response (PR) was defined as a reduction of $\geq$ 50% in the sums of the products of the perpendicular diameters of all measurable lesions for at least 4 weeks. A minor response (MR) was defined either as a reduction in the range of 25%–50% in the sums of the products of the perpendicular diameters of all measurable lesions or as a PR that did not last for >4 weeks. No change (NC) was defined as a reduction of <25% or an increase of 25% in the sums of the products of the perpendicular diameters of measurable lesions. Progressive disease (PD) was defined as the appearance of new lesions or an increase of >25% in the products of the perpendicular diameters of all measurable lesions.

Results

A total of 139 patients with nonresected primary lung cancer were recruited in this trial. Ten patients were excluded from analysis as inevaluable: three died of disease progression prior to completion of the 4-week observation period, five were excluded because of dose violations, one refused subsequent treatment after the first course and had no follow-up data available, and one was excluded because of combination treatment with other cytotoxic agents. The remaining 129 patients were fully evaluable for response and toxic effects. In all, 11 patients with stage I or II disease were included in this trial because they were $\geqq$ 80 years of age (3), had received prior chemotherapy (3), or developed complications in the CNS or the lung (5). Table 1 shows patient characteristics.

A total of 23 patients achieved a PR, but none attained a CR. The response rate for five cell types are presented in Table 2. Response rates in patients with small-cell disease, squamous-cell carcinoma, and adenocarcinoma were 28.4% (19/67), 7.1% (2/28), and 6.9% (2/29), respectively. Response rates according to dose are given in Table 3. A total of 21 patients achieved a PR at the 400 mg/m^2 dose, 17 (34.0%) with small-cell and 4 (8.5%) with non-small-cell disease, and 2 responders (11.8%) at the 300 mg/m^2 dose were observed in patients with small-cell carcinoma.

Response rates according to disease stage are shown in Table 4. In patients with small-cell disease, response rates for stages I/II, III, and IV were 50.2%, 41.2%, and 21.7%, respectively. For non-small-cell carcinoma, responders were observed in stages I/II and III. Response rates according to PS are given in Table 5. Among the patients with

Table 5. Response rates according to PS

	Patients (*n*)	CR	PR	MR	NC	PD	CR+PR patients	
Small-cell:								
PS 0	7	0	1	1	5	0	1/7	(14.3%)
1	26	0	9	1	10	6	9/26	(34.6%)
2	16	0	2	0	7	7	2/16	(12.5%)
3	18	0	7	1	5	5	7/18	(38.9%)
Non-small-cell:								
PS 0	3	0	2	0	1	0	2/3	(66.5%)
1	30	0	2	1	24	3	2/30	(6.7%)
2	23	0	0	5	11	7	0/23	(0)
3	6	0	0	2	3	1	0/6	(0)

Table 6. Response rates according to chemotherapy

	Dose (mg/m^2)	Prior chemotherapy			
		Yes		No	
Small-cell:					
	300	1/10	(10.0%)	1/7	(14.3%)
	400	6/26	(23.1%)	11/24	(45.8%)
Subtotals		7/36	(19.4%)	12/31	(38.7%)
Non-small-cell:					
	300	0/4	(0)	0/11	(0)
	400	0/11	(0)	4/36	(11.1%)
Subtotals		0/15	(0)	4/47	(8.5%)

Table 7. Toxic effects

		Incidence				Chi-square-test
		300 mg/m^2 ($n = 32$) Number of patients (%)		400 mg/m^2 ($n = 97$) Number of patients (%)		
Leukocytes:	<3,000/μl	10	(31)	50	(52)	$P < 0.1$
	<1,000/μl	0		2	(2)	
Platelets:	$<7 \times 10^4$/μl	9	(28)	51	(53)	$P < 0.05$
	$<2 \times 10^4$/μl	3	(9)	10	(10)	
Hemoglobin	<9.5 g/dl	9	(28)	35	(36)	NS
Blood urea nitrogen	>40 mg/dl	0		2	(2)	
Serum creatinine	>3.0 mg/dl	0		1	(1)	
GOT · GPT	>100 IU	1	(3)	3	(3)	
Vomiting		4	(13)	24	(25)	NS
Anorexia		9	(28)	51	(53)	$P < 0.05$
Malaise		5	(16)	20	(21)	NS
Diarrhea		1	(3)	5	(5)	
Fever		4	(13)	3	(3)	
Abdominal pain and discomfort		0		2	(2)	
Stomatitis		0		1	(1)	
Constipation		0		1	(1)	
Glossitis		0		1	(1)	
Alopecia		0		1	(1)	

NS, not significant

small-cell disease, response rates for PS 0, 1, 2, and 3 were 14.3%, 34.6%, 12.5%, and 38.9%, respectively. On the other hand, the responders with non-small-cell carcinoma were observed in PS 0 and 1, with response rates of 66.5% and 6.7%, respectively.

Response rates according to prior chemotherapy are given in Table 6. Of 31 patients with small-cell carcinoma who had received no previous chemotherapy, 1 (14.3%) achieved a PR when treated with 300 mg/m^2 carboplatin every 4 weeks, and 11 (45.8%) achieved a PR when treated at a dose of 400 mg/m^2; of 36 patients who had received prior chemotherapy, 1 (10.0%) at the 300 mg/m^2 dose and 6 (23.1%) at the 400 mg/m^2 dose achieved a PR. Of 47 patients with non-small-cell carcinoma who had received no prior chemotherapy, only 4 (11.1%) achieved a PR at a dose of 400 mg/m^2; of 22 patients who had been pretreated with cisplatin-containing regimens, 2 who had been responsive to cisplatin also responded to carboplatin.

The median duration of response in patients with small-cell and non-small-cell carcinoma was 49 days (range, 28–119 days) and 46 days (range, 28–56 days), respectively. Survival of patients with small-cell disease ranged from 4 to 180+ weeks, with a median of 27 weeks; in all, 2 patients are still alive, 60 died, and 5 were lost to follow-up. Survival of patients with non-small-cell carcinoma ranged from 4 to 154+ weeks, with a median of 37 weeks; 3 patients are still alive, 55 died, and 4 were lost to follow-up.

The most frequent side effects encountered were myelosuppression and gastrointestinal toxicity. Details are given in Table 7. A total of 60 patients (46.5%) developed thrombocytopenia, with platelet counts of $<7 \times 10^4$ μl. In all, 60 patients (46.5%) developed leukopenia, with <3,000 cells/μl. The incidence of thrombocytopenia ($<7 \times 10^4$ platelets μl) was significantly higher in patients treated with 400 mg/m^2 than in those given 300 mg/m^2 (chi-square test; $P < 0.05$). A total of 44 patients (34.1%) had anemia (hemoglobin, <9.5 g/dl). No bleeding episodes were recorded. There was not a single incidence of bacterial or fungal infection among the patients with drug-related granulocytopenia. Vomiting was mild to moderate, although 28 patients (21.7%) had at least one episode of vomiting. No renal, aural, or neurotoxicities were seen.

Discussion

In this trial, patients with nonresected primary lung cancer were treated with either 300 or 400 mg/m^2 carboplatin every 4 weeks. The majority of responses were observed at the 400 mg/m^2 dose. For small-cell cancer, the response rates at 300 and 400 mg/m^2 were 11.8% and 34.0%, respectively. The response rates in patients without and with prior chemotherapy were 38.7% and 19.4%, respectively. This result is similar to that reported by Smith et al. [9], who observed 18 responders among 30 patients without prior chemotherapy and 5 responders among 26 patients with prior chemotherapy at 300–400 mg/m^2.

For non-small-cell cancer, there were only 4 (11.1%) responders without prior chemotherapy at a dose of

400 mg/m^2. Results for non-small-cell lung cancer have been reported by Kreisman et al. [7] and Kramer et al. [6]. The former reported a response rate of 16% and the latter, that of 12%. It is of interest to note that the responders in the present trial had squamous-cell and adenocarcinoma, whereas the majority of responders reported by Kramer et al. [6] had large-cell carcinoma. A study by Olver et al. [8] showed no CRs or PRs among evaluable patients with non-small-cell lung cancer. These authors gave carboplatin at 80 mg/m^2 daily as an i.v. bolus $\times$ 5 days every 4 weeks, whereas the present study used an i.v. infusion over 1 h every 4 weeks. The possible significance of the difference in schedule is uncertain. Although carboplatin showed limited activity against non-small-cell lung cancer in our trial, we recorded 8 MR and 4 PRs; this result warrants further evaluation at higher doses of carboplatin alone or in combination with other active agents.

The response rates of 15% (21/138) for small-cell [4] and 20.3% (16/79) for non-small-cell carcinoma [2] have been reported in phase II studies of cisplatin. The response rate reported for small-cell disease represented the overall response rate for a total of eight trials, and all but four patients had received prior chemotherapy. Cisplatin is often used in combination regimens for the treatment of cancer. However, its use is limited to patients with adequate renal function, and patients must be well hydrated before and during treatment.

Carboplatin is an analog of cisplatin that lacks the severe emetogenicity, ototoxicity, and nephrotoxicity of the parent compound. With carboplatin, unlike cisplatin, transient myelosuppression is dose-limiting. In the present study, nausea and vomiting were mild to moderate and were controllable with antiemetics. The lack of nephrotoxicity precludes the need for hydration and forced diuresis, thus enabling the administration of carboplatin on an outpatient basis. In conclusion, single-agent carboplatin given at a dose of 400 mg/m^2 by i.v. infusion over 1 h every 4 weeks is recommended for the treatment of small-cell lung cancer.

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