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Cisplatin, ifosfamide and vindesine in the chemotherapy of non-small-cell lung cancer: a combination phase II study

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Summary. A total of 47 patients with unresectable non-small-cell lung cancer were treated with a regimen consisting of cisplatin (CDDP, 100 mg/m^2), ifosfamide (IFX, 2 g/m^2 × 3; with mesna) and vindesine (VDS, 3 mg/m^2) (CIV). This regimen was given over a 3- or 5-week period. Among 40 completely evaluable patients, 19 partial responses (PRs) were observed, for a response rate of 47.5% (78.6% in squamous-cell carcinoma and 30.1% in adeno- and large-cell carcinoma); no complete responses (CRs) were obtained. The hematologic toxicity was not severe, but the renal toxicity was rather high; two patients developed acute renal failure and died of subsequent pancytopenia and sepsis. We concluded that the CIV regimen was more effective, especially against squamous-cell carcinoma, but more toxic than the combination of CDDP and VDS for non-small-cell lung cancer and that candidates for this therapy must be carefully chosen.

Introduction

Although the potential combination of anti-cancer drugs such as cisplatin (CDDP) plus vindesine (VDS) or vinblastine (VBL) have recently been introduced to the chemotherapy of non-small-cell lung cancer (NSCLC) [5, 9], the treatment of advanced NSCLC remains unsatisfactory [11, 12]. To improve the overall survival of NSCLC patients treated with systemic chemotherapy, a higher response rate, a longer duration of response and a better response (a complete or nearly complete response, CR) seem to be necessary. Therefore, we designed a regimen consisting of three drugs that are active against NSCLC, namely, CDDP, ifosfamide (IFX) and VDS (CIV regimen). To evaluate the effectiveness and toxicity of this regimen, a combination phase II study was performed on patients with unresectable NSCLC.

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Patients and methods

Following the preliminary trial, in which 13 patients with NSCLC were treated with these three drugs at various doses and on different schedules, we designed a CIV regimen as follows. After overnight prehydration, 100 mg/m^2 CDDP was given intravenously over 1 or 1.5 h with 0.5 l saline. Thereafter, patients were continuously hydrated for ≥6 h with furosemide- and mannitol-induced diuresis. As antiemetics, mainly high-dose metoclopramide (7–8 mg/kg daily) and methylprednisolone (125–250 mg/day) were used. In addition, 2 g/m^2 IFX was given intravenously with 0.25 l 5% dextrose. To reduce urinary complications, patients were given the uroprotective agent mesna (sodium 2-mercapotoethane sulphonate) intravenously at 20% of the IFX dose at 0,4 and 8 h. VDS (3 mg/m^2) was given as a rapid injection. This regimen was repeated once every 3–5 weeks unless disease progressed, and dose reductions were made according to the hematologic (for VDS) and renal (for CDDP) toxicity of the preceding course of therapy.

Eligibility criteria included: (1) histologically proven NSCLC, (2) the presence of measurable lesion(s), (3) no prior therapy, (4) unresectable disease, (5) an age of 20–75 years (6) an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, (7) no other simultaneous malignancy, (8) normal bone marrow and renal functions and (9) adequate pulmonary, cardiac and hepatic functions. From June 1986 until December 1987, a total of 47 patients were entered in this study according to these criteria; their characteristics are summarized in Table 1. Among 47 registered patients, 1 who had no measurable lesion was ineligible for evaluation and 6 could not complete the treatment due to renal toxicity (n = 4), hepatic toxicity (n = 1) or doctor's protocol violation (n = 1). Thus, only 40 cases were evaluable for response.

Results

Response to chemotherapy

Responses were evaluated according to the criteria of the Japanese Lung Cancer Society. The chemotherapeutic responses of 40 evaluable patients are shown in Table 2. Although there were 11 partial responses (PRs) in 14 cases of squamous-cell carcinoma, only 8 were seen among 33 non-squamous cases. In the unmeasurable case with pleural effusion an objective response (disappearance of effusion) was obtained. The duration of response ranged between 5.0 and 33.4 weeks (median, 15.9 weeks).

Table 1. Patients' characteristics

Patients (*n*)	47	
Histology:		
Adenocarcinoma	26 } 33 nSq	
Large-cell carcinoma	7	
Squamous-cell carcinoma	14	
Treatment of patients (*n*):		
Registered	47	
Eligible	46	
Incomplete	6	
Withdrawal	5	
Dropout	1	
Complete	40	
	All (47)	nSq (33)	Sq (14)
Sex (M/F)	31/16	14/19	12/2
Age (years):			
Median (range)	62 (34–75)	62 (34–75)	55 (51–72)
<60	13 (27.7%)	11 (33.3%)	2 (14.3%)
60–75	34 (72.3%)	22 (66.7%)	12 (85.7%)
Stage:			
II	3 (6.4%)		3 (21.4%)
IIIA	13 (27.7%)	7 (21.2%)	6 (42.9%)
IIIB	10 (21.3%)	7 (21.2%)	3 (21.4%)
IV	21 (44.7%)	19 (57.6%)	2 (14.3%)
ECOG performance status:			
0	9 (19.1%)	3 (9.1%)	6 (42.9%)
1	23 (48.9%)	17 (51.5%)	6 (42.9%)
2	15 (31.9%)	13 (39.4%)	2 (14.3%)

Sq, squamous-cell carcinoma; nSq, non-squamous-cell carcinoma

Table 2. Response to chemotherapy

	All	Histology		Clinical stage			
		nSq	Sq	II	IIIA	IIIB	IV
Complete cases	40	26	14	3	12	10	15
Response:							
PR	19	8	11	2	6	6	5
NC (MR)	16 (5)	13 (5)	3 (0)	1 (0)	6 (2)	3 (2)	6 (1)
PD	5	5				1	4
Response rate (%)	47.5	30.1	78.6		50.0	60.0	33.3

nSq, non-squamous-cell carcinoma; Sq, squamous-cell carcinoma; NC, no change; MR, minor response

Table 3. Actual dose given in each treatment course

Course (*n*)	Patients (*n*)	CDDP (%)[a]	IFX (%)[a]	VDS (%)[a]	Interval (days)[b]
1st (47)	9	93.8	96.7	96.7	27 (21– 40)
2nd (38)	18	93.5	96.8	95.3	41 (21–111)
3rd (20)	7	90.8	95.1	93.0	85 (36–223)
4th (13)	9	85.4	92.9	90.7	52 (28– 61)
5th (4)	4	80.3	90.5	88.9	–
Total (122)	47				

[a] Average percentage of the projected dose
[b] Median (range)

Toxicity

As shown in Table 3, all three drugs were given at levels very near the projected dose; thus, the toxicity of this regimen was evaluated in all 47 patients over a total of 122 courses of chemotherapy.

Hematologic toxicity. As summarized in Table 4, hematologic toxicity was rather severe but controllable in the present study. Median hemoglobin, leucocyte and platelet nadirs occurred on days 14 (range, days 7–35), 13 (range, days 7–17) and 8 (range, days 3–17), respectively; recovery to normal levels required 1 or 2 weeks in almost all cases. However, cumulative toxicity seemed to occur in the later course of therapy, as dose-reductions were occasionally, necessary.

Renal and urothelial toxicity. Elevations of serum creatinine above the normal level (>1.5 mg/dl) were seen in 19 of 122 courses (Table 5). By and large, these elevations were transient, but four patients were excluded from the study during the first course because of incomplete recovery. Almost all patients showed high elevations of urinary β-2-microglobulin and NAG (*N*-acetyl-glucosaminidase) activity just after treatment (data not shown). Two patients developed acute renal failure during the first course of treatment and died of subsequent pancytopenia and sepsis. Due to administration of the uroprotective agent mesna, urinary symptoms such as hematuria and dysuria were seldom seen during treatment. Proteinuria (WHO grade 1–2) occurred in nearly all cases, appearing within the 1st week of treatment but disappearing soon thereafter.

Table 4. Hematologic toxicity

WHO grade	WBC (×1,000/mm³)	Neutrophils ×1,000/mm³)	Platelets (×1,000/mm³)	Hb (g/dl)
0	≥4.0 (3)[a]	≥2.0 (3)[a]	>100 (51)[a]	≥11.0 (9)[a]
1	3.9–3.0 (5)	1.9–1.5 (5)	99–75 (25)	10.9– 9.5 (30)
2	2.9–2.0 (26)	1.4–1.0 (8)	74–51 (18)	9.4– 8.0 (44)
3	1.9–1.0 (67)	0.9–0.5 (27)	49–25 (17)	7.9– 6.5 (27)
4	<1.0 (21)	<0.5 (79)	<25 (11)	<6.5 (12)

[a] Number of patients affected
Hb, hemoglobin

Table 5. Renal and urothelial toxicity

WHO grade	S-BUN	S-Cre	U-protein	U-blood	U-RBC
0	77	102	− (6)[a]	− (53)[a]	≤10 (101)[a]
1	32	15	±(15)	±(13)	>10 (10)
2	10	4	+(51)	+(39)	Many (9)
3	1	0	2+ (8)	2+ (8)	Countless (1)
4	2	1	3+ (7)	3+ (7)	

[a] Number of patients affected
S-BUN, serum blood urea nitrogen; S-Cre, serum creatinine; U-protein, proteinuria; U-blood, hematuria (hemoglobin); U-RBC, hematuria (red blood cells)

Other toxicities. Nausea and vomiting were well controlled during the first 3 days of therapy by high-dose metoclopramide and methylprednisolone. However, almost all patients experienced nausea and vomiting (WHO grade 2–3) in subsequent days, with a loss of appetite lasting for 1 or 2 weeks. Alopecia (WHO grade 2–3) was commonly seen in all subjects. One patient with diabetes developed peripheral neuropathy (WHO grade 2) during the first course of therapy.

Survival

The median survival for all patients was 13 months (range, 0.4–40.8 months). The survival curves are illustrated in Fig. 1 according to the Kaplan-Mayer method. Although evaluation of survival was not the main purpose of this phase II study, a significant difference in survival was observed between the squamous and non-squamous cases (20.1 vs 9.5 months).

Discussion

In the chemotherapy of advanced NSCLC, the introduction of CDDP and VDS has resulted in a relatively high response rate [5, 9]. However, there is little evidence that shows how systemic chemotherapy consisting of these drugs could provide survival benefit to patients with advanced NSCLC [11, 12]. Therefore, several trials were performed to prove the superiority of a three drug combination (i.e. CDDP + VDS/VBL + drug X). No compared except mitomycin C has shown efficacy as the third agent in this regimen [7, 8, 10]. It has recently been reported in a number of phase II studies [6, 13] that IFX is one of the most active single agents against NSCLC; however, few studies have clarified the significance of IFX in combination chemotherapy [1, 2]. Thus, we performed the present combination phase II study.

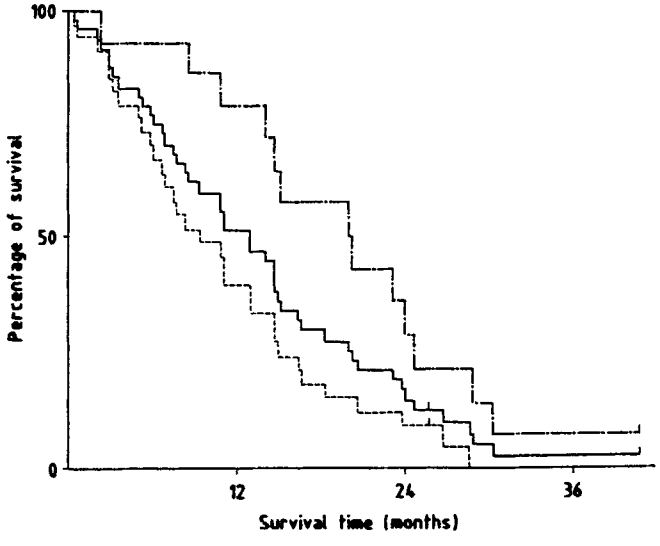

Fig. 1. Survival curve for patients treated with CIV: overall median survival (———), 13 months; median survival of patients with squamous-cell carcinoma (— — —), 20.1 months; median survival of subjects with non-squamous-cell carcinoma (– – – –), 9.5 months

In the present study this regimen showed a relatively better response rate (47.5%) in patients with unresectable NSCLC than that obtained with CDDP and VDS. In squamous cases, the high response rate of 78.6% may have contributed to the prolongation of survival in this study. However, it should be indicated that patients in this group had better prognostic factors than did the non-squamous group. Further studies including patients with more advanced disease seem necessary for evaluation of the efficacy of this regimen against squamous-cell carcinoma. On the other hand, the response rate in patients with non-squamous-cell-cancer (adeno- and large-cell carcinoma) was at best the same as those previously reported. For this kind of lung cancer, the design of a more powerful combination regimen or introduction of a new type of treatment modality seems necessary.

The side effects caused by the present regimen were also higher than those induced by a two-drug combination. Setting bone marrow toxicity aside, we emphasized tubular nephrotoxicity attributable to the combination of CDDP and IFX. Mesna is a uroprotective agent that can neutralize the toxic products of IFX in the bladder. Due to the use of this uroprotector, no hemorrhagic cystitis or dysuria was seen in our patients. However, extremely high elevations of urinary NAG and β-2-microglobulin were observed in almost all patients, which means that Mesna cannot work in the renal tubules. As expected from previous reports [3, 4], tubular toxicity seemed to be synergistic or at least additive on this regimen.

In conclusion, the CIV regimen is likely to be more effective for NSCLC, especially in squamous-cell carcinoma, than the combination of CDDP and VDS. However, the toxicity of this regimen, particularly the tubular nephrotoxicity, is higher than that induced by the two-drug combination. To make this particular therapy beneficial, candidates for treatment must be carefully selected.

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