Prospective Evaluation of the Feasibility of Cisplatin-based Chemotherapy for Elderly Lung Cancer Patients with Normal Organ Functions

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A study was conducted to examine the feasibility of cisplatin-based chemotherapy in elderly patients (≥ 75 years old) with advanced non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC). Thirty-four patients were enrolled between September 1993 and December 1994. Patients with normal organ function and good performance status (PS) received cisplatin-based chemotherapy (cisplatin 80 mg/m^2 on day 1 and vindesine 3 mg/m^2 on days 2 and 8 for NSCLC, or cisplatin 80 mg/m^2 on day 1 and etoposide 100 mg/m^2 on days 2 to 4 for SCLC). Ten patients (29%) were eligible for this study, 7 with NSCLC and 3 with SCLC. Reasons for exclusion were ischemic heart disease in 14, poor PS (≥ 2) in 11, reduced creatinine clearance (Ccr) in 10, abnormal electrocardiogram without ischemia in 9 and noncompliance with the protocol in 2 patients. Eight patients had two or more reasons. Nine of the 10 eligible patients were able to tolerate 2 or more courses of chemotherapy. All 3 patients with SCLC responded (1 complete response and 2 partial response), but only 1 of the patients with NSCLC achieved partial response. Toxicity was evaluated according to Japan Clinical Oncology Group criteria. All but one patient experienced grade 4 neutropenia, and 6 patients had infectious episodes requiring antibiotics. Grade 3 anemia and thrombocytopenia were observed in 1 and 2 patients, respectively. Non-hematological toxicities were mild. Only 10 of 34 patients (29%) satisfied our eligibility criteria and they experienced severe myelotoxicity. We conclude that chemotherapy should be given carefully to elderly patients even if they appear to have normal organ function.

Key words: Elderly patient — Cisplatin — Lung cancer

Lung cancer and resultant mortality are increasing in incidence. As the average life span lengthens, the number of elderly lung cancer patients is increasing in Japan. The combination of cisplatin plus etoposide is a standard chemotherapy regimen for small cell lung cancer (SCLC),[1] and cisplatin plus a vinca alkaloid is believed to be one of the most effective combination chemotherapy regimens for non-small cell lung cancer (NSCLC), in spite of its small impact on survival.[2] There have, however, been few prospective studies to determine whether SCLC or NSCLC patients over 75 years old can tolerate these standard regimens. It is generally believed that elderly patients are less able to tolerate aggressive chemotherapy than their younger counterparts. Bone marrow cellularity diminishes with age and elderly patients may have decreased tolerance to myelosuppressive agents.[3] The function of vital organs such as the liver or kidney declines with age, and the ability to catabolize and excrete drugs is reduced, resulting in a greater likelihood of toxicity.[3] Based on these observed physiologic changes associated with aging, it is reasonable to anticipate that the toxicity of anticancer therapy may be more

marked in elderly patients. Indeed, elderly patients are often excluded from clinical trials for this reason. In a review of 19 Eastern Cooperative Oncology Group (ECOG) trials treating advanced cancer in eight disease sites, toxic reactions in older patients were shown to be slightly more common than those observed in similarly treated younger patients.[4] On the other hand, in a study of treatment in 223 SCLC patients aged between 29 and 78 years, patients of all ages were found to benefit from treatment, while an initially poor performance status (PS), but not age or the extent of disease, was significant in predicting sudden/toxic death.[5] We have also previously reported no correlation between myelotoxicity and age during chemotherapy in 183 NSCLC patients.[6] In an analysis of cisplatin-induced nephrotoxicity in 43 cancer patients aged between 29 and 77 years, it was reported that cisplatin dose changes or schedule modifications were not indicated on the basis of advancing age.[7]

Therefore, we hypothesized that elderly lung cancer patients with good PS, adequate organ function, and without background complications would be able to tolerate standard cisplatin-based chemotherapy. We conducted this feasibility study to determine whether elderly patients with good PS and normal organ function could

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receive cisplatin at a dose of 80 mg/m² in combination with other agents without toxicity.

PATIENTS AND METHODS

Patients Between September 1993 and December 1994, 34 elderly patients with histologically or cytologically proven advanced NSCLC or SCLC were enrolled and their eligibility to receive cisplatin-based chemotherapy was examined. The characteristics of these patients are summarized in Table I. There were 4 patients with poor PS (ECOG criteria 3 or 4). Twenty-five patients (74%) were heavy smokers (smoking index ≥400). Weight loss of over 5% of body weight during the 3 months before registration was observed in 12 patients (35%). Six patients (18%) had synchronous double cancer as shown in

Table I. Characteristics of Enrolled Patients

		No. of patients
Total patients		34
Age (years)		
median		78
range		75–89
Sex		
male		25
female		9
Performance status (ECOG)		
0		5
1		19
2		6
3		3
4		1
Prior treatment		
surgery		2
radiotherapy		3
none		29
Smoking (index ≥400)		25
Weightloss (≥5%/3 mo)		12
Pathology		
adenocarcinoma (ad)		19
small cell carcinoma (sm)		7
squamous cell carcinoma (sq)		9
others		3
(double[a])		6)
Stage		
small cell	LD	3
	ED[b]	4
non-small cell	IIIA	3
	IIIB	4
	IV	14
	recurrence	2
	double	5

Smoking index = (years of smoking) × (cigarettes/day).
a) Double cancer: ad+sq (3), sq+sq (1), sm+sq (1), ad+gastric cancer (1).
b) One patient had sm plus sq.

Table I. Complications in enrolled patients included cardiac complications in 20 patients (59%); hypertension (9), ischemia (6), valve disease (4) and myopathy (1). One patient had a history of cerebral infarction. Table II shows cardiac and renal functions in the enrolled patients. A normal electrocardiogram (ECG) was found in only 11 patients (32%). Ten patients had a clinically significant reduction in creatinine clearance (Ccr) over 24 h (<60 ml/min).

Eligibility criteria for cisplatin-based chemotherapy were as follows: an expected survival of at least 6 weeks, measurable lesions, ECOG PS score ≤1, white blood cell count (WBC) ≥4,000/μl, hemoglobin ≥10 g/dl, platelet count ≥100,000/μl, total serum bilirubin <1.5 mg/dl, serum aspartate aminotransferase (SGOT) and alanine aminotransferase (SGPT) less than twice the normal range, serum creatinine ≤1.5 mg/dl, Ccr more than 60 ml/min, normal ECG, normal single master ECG, ejection fraction of left ventricles on ultrasound cardiogram (UCG) more than 55%, PaO₂ ≥70 Torr. None of the patients had received prior chemotherapy for their primary lesion. Written informed consent was obtained in every case.

Chemotherapy All patients except those with disease progression were treated twice with cisplatin 80 mg/m² on day 1 plus vindesine 3 mg/m² on days 2 and 8 for NSCLC or cisplatin 80 mg/m² on day 1 plus etoposide 100 mg/m² on days 2 to 4 for SCLC. Etoposide was infused i.v. over 1 h in 250 ml of 5% glucose. Vindesine was given as an i.v. bolus. Cisplatin was given over 1 h after prehydration with 1 liter of 2.5% glucose in 0.45% NaCl with

Table II. Cardiac and Renal Function in the Elderly Patients Enrolled

		No. of patients
ECG	Ischemic change	14
	Left ventricular hypertrophy	3
	Atrial arrythmia	3
	Bundle branch block	3
	Normal[a]	11
UCG	Abnormal ejection fraction (<60%)	1
Ccr (ml/min)	30–39	1
	40–49	5
	50–59	4
	60–69	5
	70–79	7
	80–	9
	unknown	3

ECG, electrocardiogram; UCG, ultrasound cardiogram; Ccr, creatinine clearance over 24 h.
a) No patient with normal ECG at rest showed a positive abnormality in the master test.

20 mEq K$^+$/liter. Following administration of cisplatin, patients received mannitol (20%) i.v. at a rate of 50 ml/h over 6 h and 2 liter of 2.5% glucose in 0.45% NaCl with 20 mEq K$^+$/liter at a rate of 200 ml/h. To control cisplatin-induced emesis, patients received an i.v. infusion of 3 mg of granisetron plus 16 mg of dexamethasone. Physical examinations, complete blood counts, biochemical tests and chest roentgenograms were performed weekly for the first 8 weeks of treatment and every 2–4 weeks thereafter. The criteria for response were as follows. Complete response (CR) was defined as the complete disappearance of all evidence of tumor for at least 4 weeks. Partial response (PR) was defined as at least a 50% reduction of the sum of the product of the two greatest perpendicular diameters of all indicator lesions for at least 4 weeks, with no appearance of new lesions or progression of any existing lesions. Disease progression (PD) was defined as at least a 25% increase in tumor area or the appearance of new lesions. All other outcomes were classified as no change (NC). Toxicity was evaluated according to Japan Clinical Oncology Group (JCOG) criteria.[8] The Institutional Review Board (IRB) of the National Cancer Center of Tokyo reviewed and approved the protocol prior to commencement.

RESULTS

Ten patients (29%) were eligible for this study. Three patients had SCLC and one of 4 patients with double cancer had small cell carcinoma plus squamous cell carcinoma (Table III). The patient with small cell and squamous cell carcinoma was treated with cisplatin and etoposide. Reasons for exclusion were ischemic heart disease in 14, poor PS ($\geq$2) in 11, reduction in Ccr in 10, abnormal ECG without ischemia in 9 and noncompliance in 2 patients. Eight patients had two or more reasons for exclusion (Table IV). The outcome of chemotherapy in

Table III. Characteristics of Eligible Patients

	No. of patients
Eligible patients	10
Sex (male/female)	8/2
Performance status (0/1) (ECOG)	3/7
Serum albumin (g/dl)	
mean	3.6
range	3.2–4.0
Pathology[a]	
small	3
non-small	7
(double[b]	4)

a) Pathology of main tumor.
b) There were 4 patients with double cancer.

the 10 patients is shown in Table V. All 3 patients with SCLC responded (1 CR and 2 PR), but only 1 of the patients with NSCLC achieved PR. All but one patient experienced grade 4 neutropenia and 6 had an infection requiring antibiotics. A neutrophil nadir below 100/μl during the first course was observed in 7 patients (mean 96/μl, range 0–546/μl). Grade 3 anemia and thrombocytopenia were observed in 1 and 2 patients, respectively. Non-hematological toxicities were mild. We also examined changes in PS and the time for which patients were unable to eat normally as feasibility criteria for cisplatin-based chemotherapy. No patients experienced

Table IV. Reasons for Exclusion

	No. of patients
Ischemic heart disease	14
Poor performance status ($\geq$2)	11
Reduction in Ccr ($<$60 ml/min)	10
Abnormal ECG without ischemia	9
Noncompliance	2

Eight patients had several reasons.
Ccr: Creatinine clearance over 24 h.

Table V. Outcome of Chemotherapy

		No. of patients
Response		
small	CR	1
	PR	2
non-small	PR	1
	NC	5
	PD	1
Toxicities		
Leukocyte	grade 3	4
	grade 4	2
Neutrophil.	grade 3	1
	grade 4	9
Hemoglobin	grade 3	1
Platelet	grade 3	2
Infection		6
Emesis	grade 2	3
Treated for 2 or more courses		9

	Months
Median duration of response (range)	
small	5.2 (4.2–6.4)
non-small	2.0
Median survival time (range)	
small	12.7 (10.5–14.6)
non-small	12.0 (6.4–18.7$^+$)

Toxicity assessed by JCOG criteria. CR, Complete response; PR, partial response; NC, no change; PD, progression of disease.

PS 3 or 4 during chemotherapy, though 7 days or more were required to resume the level of food intake normal before chemotherapy in 6 of 10 patients. Nine patients received 2 or more courses of chemotherapy (range 2 to 4); however, modifications in the second course of chemotherapy were required in 4 patients, i.e., the total cisplatin dose was given over 4 days in 3 patients because of poor appetite during the 1st course, and vindesine or etoposide was reduced to 75% of the original dose in 2 patients because of severe myelosuppression.

DISCUSSION

In general, these elderly patients experienced more severe toxicity but a similar respose and survival compared with younger populations during cancer chemotherapy.[4, 5] We selected lung cancer patients with normal organ function and good PS, and treated them with a standard dose and schedule of cisplatin. Most of the enrolled patients had several ineligibility criteria and were excluded. The important reasons for exclusion were heart disease, renal dysfunction and poor PS. Only 10 of 34 patients were able to receive a bolus infusion of cisplatin at the full dose of 80 mg/m^2. Nine of the 10 patients experienced grade 4 neutropenia and 6 patients had an infection requiring antibiotics, but no sepsis was observed. Toxicities other than myelosuppression were mild and almost no damage to cardiac, pulmonary, renal or liver function was observed. This suggested that selected patients with normal organ function and good PS would be able to tolerate treatment in spite of requiring support for myelotoxicity.

Only patients with good PS (ECOG criteria 0 or 1) were eligible for this study. A retrospective analysis of elderly patients with aggressive non-Hodgkin's lymphoma supported this decision.[9] In our retrospective analysis of treatment in 14 SCLC patients with PS 3 or 4, chemotherapeutic death was observed in two patients (unpublished data). We also found that febrile episodes were frequent when the neutrophil nadir was below 100/μl.[10] In the present study, 7 of 10 patients experienced a neutrophil nadir below 100/μl as a result of myelotoxicity in spite of having a PS of 0 or 1. It is therefore questionable whether elderly patients with PS 2 or more would be able to tolerate cisplatin-based myelotoxic chemotherapy.

A decline in the function of vital organs such as the liver and kidneys may reduce the efficiency of drug metabolism and excretion, resulting in a greater incidence of toxicity. We previously reported that age was a consistent, independent and significant predictor of the area under the concentration curve (AUC) of ultrafiltrable platinum.[11] Ccr decreased with aging, but both Ccr and age were independent factors for predicting the AUC of cisplatin. The AUC of cisplatin in elderly patients was higher than in young patients.[11] It is suggested that the higher AUC of platinum may induce severe neutropenia in elderly patients. We used 50 μg/m^2 granulocyte colony-stimulating factor (G-CSF) for patients whose leukocyte count fell to less than 2,000/μl or whose neutrophil count fell to less than 1,000/μl. The criteria for G-CSF use in chemotherapy for elderly patients should be modified to allow the prevention of severe neutropenia. Possibly, prophylactic oral antibiotics such as trimethoprim/sulfamethoxazole may also be useful.[12]

Four of the 10 eligible patients in the present study had synchronous double cancer. It is possible that a higher susceptibility to DNA-damaging agents in cancer patients favors tumor development, and synchronous double cancer occurs with considerably high frequency in elderly patients. Treatment should be carefully chosen for synchronous double cancer; for instance, we must consider whether patients should be given a combination of local therapies for each cancer type or whether general chemotherapy is indicated.

Only 10 of 34 patients (29%) satisfied the eligibility criteria and they experienced severe myelotoxicity. We conclude that chemotherapy should be given carefully to elderly patients even if they appear to have normal organ function.

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