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Cisplatin-based combination chemotherapy for elderly patients with non-small-cell lung cancer

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Abstract *Purpose*: To compare the response rates, toxicities and survival durations of elderly patients (70 years of age or more) with those of younger patients (less than 70 years of age) with non-small-cell lung cancer (NSCLC) treated with cisplatin-based chemotherapy. *Patients and methods*: We analyzed retrospectively the data of 203 assessable patients entered on a prospective randomized trial of cisplatin-based combination chemotherapy. Chemotherapy consisted of three dosage regimens: (1) vindesine and cisplatin (VP); (2) mitomycin, vindesine and cisplatin (MVP); or (3) etoposide and cisplatin alternating with vindesine and mitomycin (EP/VM). *Results*: A greater proportion of elderly patients had localized disease and more squamous cell carcinoma than non-elderly patients. The overall response rates were 44% in the elderly group and 28% in the non-elderly group. In the EP/VM arm, the response rate was significantly better in the elderly group than in the non-elderly group. The frequency of grade 4 leukocytopenia in the MVP and EP/VM arms in the elderly group was significantly greater than in the non-elderly group ($P < 0.05$). No differences were found in nonhematological toxicities between the two groups. There was no difference in overall survival between the groups. *Conclusion*: Elderly patients treated with mitomycin-containing regimens have higher hematologic toxicities than younger patients. The results of this study are consistent with the previously reported pharmacologic data on mitomycin suggesting altered pharmacokinetics in elderly patients. The improved response rate in the elderly patients was probably because more elderly patients had earlier disease, squamous cell carcinoma and better performance status. Cisplatin-based chemotherapy was tolerable for most elderly NSCLC patients with good performance status.

Key words Non-small-cell lung cancer · Elderly · Chemotherapy · Cisplatin · Mitomycin-C

Introduction

The population of Japan and western countries is gradually aging. Since cancer is a disease of older persons, the incidence of cancers is expected to increase during the coming decades. It has been estimated that up to one-third of cancers occur in individuals older than 70 years [1, 11]. Lung cancer is a major problem in industrialized countries in the world and a growing problem in developing countries. Presently, lung cancer is the second most common cause of cancer death in Japan, and it has been estimated it will be the most common cause of cancer death in the next decade [25].

Non-small-cell lung cancer (NSCLC) accounts for 80% of all lung cancers. Recent meta-analysis of chemotherapy in metastatic NSCLC revealed a small but significant survival benefit from cisplatin-based chemotherapy [19]. For selected patients in stage III NSCLC, combined modality treatment comprising cisplatin-based chemotherapy and radiotherapy has become the standard [3, 12, 13, 21, 22]. Thus, cisplatin-based chemotherapy has potential benefit for elderly patients with NSCLC. Patients older than 70 years have been excluded from many clinical trials of cancer treatment, so there has been little information on therapeutic management in this age group. To evaluate the difference of response and toxicities of cisplatin-based chemotherapy by age, we analyzed patients enrolled into a prospective

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randomized trial [5]. The objectives of this study were to evaluate the differences in response, survival and toxicity outcomes between elderly and younger patients with NSCLC treated with cisplatin-based combination chemotherapy.

Material and methods

Eligibility

Criteria for the prospective study included the following: cytologic or histologic diagnosis of NSCLC, unresectable stage IIIA, IIIB or IV, measurable lesions, age less than 75 years, performance status less than 3 on the Eastern Cooperative Oncology Group (ECOG) scale, adequate pretreatment renal function (serum creatinine < 1.5 mg/ml), adequate hepatic function (AST less than twice the upper limit of normal value), adequate bone marrow function (WBC count $\geqq 4000/\mu l$, platelet count $\geqq 100\,000/\mu l$), and normal cardiac function (no acute myocardial infarction, no signs of congestive heart failure, and no serious arrhythmias), no prior chemotherapy or radiotherapy, no concurrent active malignancies, and provision of informed consent. Stage IIIA disease was included only if it was incurable by surgery for the following reasons: (1) mediastinal lymph node involvement seen on a plain chest roentgenogram, (2) extension to within 2 cm of a main stem bronchus, (3) extensive invasion of the chest wall, or (4) any combination of these factors.

The initial evaluation consisted of a complete history and physical examination, blood chemistries including complete blood counts, electrolytes, blood urea nitrogen, serum creatinine, liver function tests, urinalysis, and ECG. Patients were staged with routine chest roentgenography, whole-lung tomography, fiberoptic bronchoscopy, computed tomography of the head and abdomen, and bone scintigraphy. Computed tomographic scan of the chest was not used to stage the patients with reference to the mediastinum, and mediastinoscopy was not performed to confirm the presence of mediastinal lymph node metastasis. The New lnternational Staging System for Lung Cancer was used for stage classification [18]. For stratification, we defined limited disease as stage IIIA or IIIB without malignant pleural effusion or contralateral supraclavicular lymph nodes. Extensive disease was defined as stage IV or tumor with malignant pleural effusion or contralateral supraclavicular lymph nodes. Blood chemistries, chest roentgenographs, and clinical examination results were recorded weekly.

Treatment

After stratification for limited versus extensive disease patients were randomly assigned to receive one of the following combination chemotherapy treatment regimens (arms): vindesine 3 mg/m^2 intravenously (IV) on days 1, 8, 15, 29, 36, and 43, and cisplatin 100 mg/m^2 IV on days 1 and 29, repeated every 4 weeks (VP); or mitomycin 8 mg/m^2 IV on days 1 and 29, vindesine 3 mg/m^2 IV on days 1, 8, 29, and 36, and cisplatin 80 mg/m^2 IV on days 1 and 29, repeated every 4 weeks (MVP); or cisplatin 80 mg/m^2 IV on day 1, etoposide 100 mg/m^2 IV on days 2, 4, and 6, vindesine 3 mg/m^2 IV on days 22 and 29, and mitomycin 10 mg/m^2 IV on day 22, repeated every 6 weeks (EP-VM). Patients who received cisplatin were hydrated on day 1 with 2600 ml 5% dextrose in 0.45% sodium chloride IV to induce diuresis. In each group, subsequent doses were reduced to 75% of the initial dose if the leukocyte nadir decreased to less than 1000/μl or the platelet nadir was $\leqq 30\,000/\mu l$.

Doses were also modified as needed for renal dysfunction. After completion of chemotherapy, each patient was restaged with all the tests used during the initial workup. In accordance with the World Health Organization (WHO) criteria [14], the responses and toxicities were reviewed and classified during regular meetings of a group consisting of the study investigators and at least two extramural observers.

Study design, statistical analysis, and quality control

We retrospectively analyzed and compared those aged less than 70 years (non-elderly) with those aged 70 years or more (elderly) in regard to study parameters including sex, ECOG performance status, histology, stage of disease, chemotherapy regimen, response rate, toxicities and survival. Survival time was measured from the date of the first treatment to the date of death, or recorded as alive to date of most recent follow-up. Actuarial survival curves were calculated by the method of Kaplan and Meier [10] and were compared for statistical significance using the generalized Wilcoxon test [6]. Chi-squared tests were used to assess the significance of differences of between proportions. The Statistical Application System (SAS) [23] was used for multivariate analysis of variables for grade 4 leukocytopenia according to a logistic regression model [27].

Results

Of 210 patients entered onto the trial, 199 were evaluable for response and 203 for toxicities. Five non-elderly patients were withdrawn before therapy; one patient died, and four refused the therapy. Two non-elderly patients were deemed ineligible because of lack of proof of NSCLC and concurrent other malignant tumor. Characteristics of the elderly and non-elderly patients are listed in Table 1. The elderly and non-elderly patients were evenly distributed by sex and treatment arm. There was a slightly higher proportion of patients with a good performance status (PS 0,1) in the elderly group ($P = 0.1232$). Adenocarcinoma was the most common cell type among the non-elderly group and squamous cell carcinoma was most common among the elderly group ($P = 0.0107$). More limited disease was found in the elderly group than the non-elderly group ($P = 0.0572$). There were significant differences between the two groups regarding performance status in the EP/VM arm, stage in the MVP arm and disease extent in the VP arm ($P < 0.05$).

Of the 203 patients, four (two in the elderly group and two in the non-elderly group) were not assessable for response, two because of early death, one because of inadequate assessment of response, and one because of treatment discontinuation. The response rates, by age and treatment arm are listed in Table 2. The overall response rate (complete and partial response) was 28% in the non-elderly group and 44% in the elderly group. In the EP/VM arm, the response rate was significantly better in the elderly group than the non-elderly group ($P = 0.029$). There were no differences in the response rates in the VP and MVP arms according to age. The incidence of WHO grade 2 or higher toxic reactions is listed in Table 3. No deaths were judged to be treatment-related. The frequency of grade 4 leukocytopenia in the elderly group was greater than that in the non-elderly group ($P = 0.07$). The difference was profound in the

Table 1 Patient characteristics

	All		VP		MVP		EP/VM	
	Non-elderly	Elderly	Non-elderly	Elderly	Non-elderly	Elderly	Non-elderly	Elderly
No. of eligible patients	160	43	53	14	51	17	56	12
Sex								
Male	125	31	41	11	39	12	45	8
Female	35	12	12	3	12	5	11	4
Performance status								
0–1	107	34	44	9	26	13	37	12
2	53	9	9	5	25	4	19*	0*
Histology								
Squamous cell carcinoma	62*	26*	23	9	17	9	22	8
Adenocarcinoma	83	15	27	5	30	7	26	3
Large cell carcinoma	15	2	3	0	4	1	8	1
Stage								
IIIA	58	21	22	7	18	8	18	6
IIIB	29	7	5	3	14	0	10	4
IV	73	15	26	4	19	9	28	2

*$P < 0.05$

Table 2 Overall response rate

	All		VP		MVP		EP/VM	
	Non-elderly	Elderly	Non-elderly	Elderly	Non-elderly	Elderly	Non-elderly	Elderly
No. of assessable patients	158	41	51	12	51	17	56	12
Complete response	1	1	0	0	0	1	1	0
Partial response	44	17	16	5	21	7	7	5
No change	83	18	28	4	21	8	34	6
Progression	30	5	7	3	9	1	14	1
Response rate (%)	29	44	31	42	41	47	14*	42*

*$P < 0.05$

Table 3 Toxicities WHO grade 2 or higher (%). Numbers in parentheses are the percentage of patients with WHO grade 3 or 4 toxicity

	All		VP		MVP		EP/VM	
	Non-elderly [$n = 160$]	Elderly [$n = 43$]	Non-elderly	Elderly	Non-elderly	Elderly	Non elderly	Elderly
Bone marrow								
Leukopenia	90 (67*)	93 (86*)	94 (74)	93 (86)	92 (73)	94 (88)	84 (55)	92 (83)
Grade 4 leukopenia	18	37	17	14	24*	53*	14*	42*
Thrombocytopenia	29 (14)	42 (21)	17 (2)	14 (14)	39 (20)	53 (24)	30 (16)	58 (25)
Anemia	63 (31)	77 (35)	74 (40)	71 (38)	59 (27)	76 (35)	57 (25)	83 (33)
Grade 3 or 4 hematologic toxicity (%incidence)	73	88	81	93	77	88	63	83
Renal								
Createnine	4	2	4	0	8	6	0	0
BUN	11 (3)	12 (2)	13 (4)	14	14 (2)	18 (6)	7 (2)	0
Hepatic								
AST	5	2	9	7	2	0	4	0
ALT	7	2	11	7	2	0	5	0
Neuropathy								
Peripheral	2	5 (2)	2	7 (7)	0	6	4	0
Nausea & vomiting	42 (15)	49 (14)	45 (13)	71 (21)	41 (20)	59 (12)	39 (13)	12 (8)
Mucositis	3	5	2	0	4	6	2	8
Diarrhea	4 (2)	0	9 (2)	0	2	0	2 (2)	0
Alopecia	57	60	49	71	55	53	66	67
Grade 3 and 4 nonhematologic toxicities (%incidence)	16	19	15	29	20	12	13	8

*$P < 0.05$

Table 4 Multivariate analysis: probability of grade 4 leukocytopenia in patients in the MVP or EP-VM arm determined by a logistic model. All variables are pretreatment factors except for number of chemotherapy cycles

Variable	*a*	*P*-value	SE	Odds ratio
Age (< 70, ≥ 70 years)	1.2046	0.0228	0.551	3.336
Body surface area (< 1.5, ≥ 1.5 m^2)	−0.816	0.1089	0.509	0.442
Serum creatinine (≤ 1.0, > 1.0 mg/ml)	−0.2618	0.7136	0.7134	0.77
Hemoglobin (< 12, ≥ 12 g/dl)	0.0343	0.9411	0.4644	1.035
WBC (< 6000, ≥ 6000/m^3)	0.4643	0.3728	0.521	1.591
Stage of disease (III, IV)	−0.4596	0.3308	0.4726	0.632
Sex (male, female)	0.261	0.621	0.5279	1.298
Performance status (0 + 1, 2)	0.0164	0.9761	0.549	1.017
LDH (not elevated, elevated)	0.81	0.1226	0.5246	2.248
ALT (≤ 40, > 40 U/l)	−0.4446	0.6173	0.8897	0.641
Weight loss (≥ 10, < 10%)	−0.4213	0.4647	0.5763	0.656
Number of chemotherapy cycles (1 + 2, 3 ≤)	0.0215	0.9805	0.8787	1.022

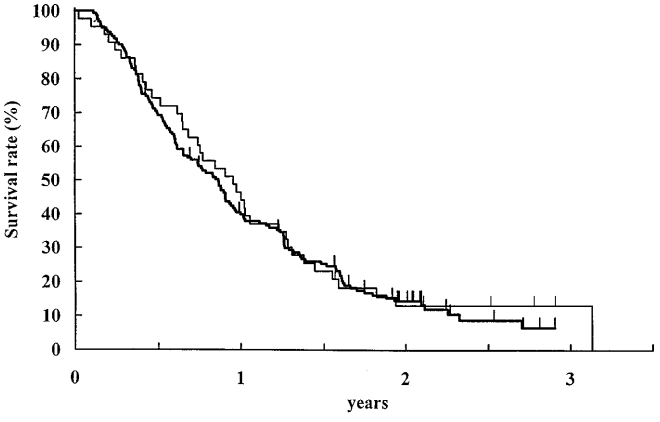

Fig. 1 Overall survival: — elderly group, 43 patients, median survival time, 50 weeks; — non-elderly group, 160 patients, median survival time, 43 weeks. ($p = 0.6549$)

MVP and EP/VM arms with 53% and 42% of grade 4 leukocytopenia in the elderly group and 24% and 14% in the non-elderly group, respectively ($P < 0.05$). There were no differences in the toxicities in the VP arm. No differences were found in nonhematological toxicities between the two groups.

A multivariate analysis of the incidence of grade 4 leukocytopenia, using a logistic model, showed that age ($P = 0.02822$) was of independent prognostic significance in patients treated with mitomycin-containing regimens (Table 4). Age was not a significant factor for grade 4 leukocytopenia in patients treated with the VP regimen ($P = 0.3067$). In all eligible patients, age ($P = 0.0427$) and weight loss ($P = 0.0096$) were of prognostic significance for grade 4 leukocytopenia using a stepwise selection procedure. Multivariate analysis for grade 4 leukocytopenia failed to show any significant factors in elderly patients treated with mitomycin-containing regimens. The overall survival curves of both groups are shown in Fig. 1. The median survivals were 50 weeks for the elderly group and 43 weeks for the non-elderly group; the difference was not significant.

Discussion

Unlike most cancers, lung cancer is significantly more likely to have lower stage disease at the time of diagnosis in elderly patients than in younger patients [7, 8]. Teeter et al. reported that the proportion of squamous cell carcinoma increases with increasing age, whereas the proportion of adenocarcinoma and small-cell undifferentiated carcinoma decreases with increasing age [24]. In the present study there were more patients with squamous cell carcinoma and stage III disease in the elderly group, which is consistent with earlier findings.

Although a recent meta-analysis has shown a significant survival benefit for patients receiving chemotherapy for advanced NSCLC, its routine use is still controversial given the poor long-term survival results and toxic nature of the treatment. In two of the randomized trials which compared supportive care with chemotherapy in mainly stage IV disease, the overall survival was significantly prolonged by cisplatin-based chemotherapy, and the 1-year survival rates were 21% to 22% for chemotherapy versus 10% for supportive care [20] and 38% for chemotherapy versus 12% for supportive care [2]. In stage III disease there have been several randomized trials showing significant survival benefit from cisplatin-based combination chemotherapy plus chest irradiation when compared with chest irradiation alone [3, 13, 21, 22]. The Cancer and Leukemia Group B (CALGB) trial reported by Dillman et al. [3] is the most striking one in which 155 patients with inoperable or unresectable stage III NSCLC were randomized to receive radiation alone or two cycles of cisplatin and vinblastine followed by radiation therapy. The median survival time and 3-year actuarial survival was 14 months and 23% for those who received induction chemotherapy versus 10 months and 11% for those who received radiotherapy alone ($P = 0.0066$). A recent update revealed a 5-year survival rate of 17% for the induction chemotherapy group versus 6% for radiotherapy alone group [4]. The Radiation Therapy Oncology Group (RTOG) and ECOG have recently

reported a study that tested the combined arm of the CALGB trial versus twice-daily hyperfractionated radiation to a total of 69.6 Gy, versus a control arm of conventional radiation to 60 Gy [21]. The results of this study confirm the survival advantage for the combined modality approach.

Combining non-cisplatin-containing chemotherapy with radiotherapy has not yielded a survival benefit in this patient group [9, 15, 17, 26]. Thus, combined radiation and cisplatin-based chemotherapy has been accepted as standard care in selected patients who have unresectable locally advanced NSCLC. Because elderly patients are more likely to present with localized disease, it is important to evaluate outcome in elderly patients who received cisplatin-based combination chemotherapy.

Miya et al. reported that the area under the time versus concentration curve of mitomycin increased significantly with the age of patients [16]. In the present study, the frequency of grade 4 leukocytopenia in elderly patients treated with mitomycin-containing regimens was significantly greater than in non-elderly patients. These results could be explained in part by the differences in mitomycin pharmacokinetics. In the EP/VM arm, the response rate was significantly better in the elderly group than in the non-elderly group. This result was probably because more elderly patients had earlier disease, squamous cell carcinoma and better performance status.

It is unclear whether age, per se, is always associated with an increase in toxicities such as mucositis, nausea and vomiting, cardiotoxicity and neurotoxicity. Nonhematological toxicity and survival were similar in both groups in the present study. Because the imbalance of performance status suggests there was an implicit age bias to enroll patients on the study, we must be careful in applying these results to all elderly patients. However, it is suggested that elderly patients who meet the eligibility criteria with good performance status could have a similar benefit to younger patients.

The present study indicates the importance of the pharmacological study of elderly patients who enter investigational clinical trials. Elderly NSCLC patients with good performance status should be included in future experimental studies of chemotherapy to determine whether such findings can be translated to clinical advantage.

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