Table 6. Median Survival Time and 1-Year Survival According to Clinical Factors

Variable	Chemotherapy Naive			Previously Treated With Chemotherapy		
	No. of Patients	Median Survival Time (days)	1-Year Survival Rate (%)	No. of Patients	Median Survival Time (days)	1-Year Survival Rate (%)
Sex						
Female	131	481	64.0	500	502	61.9
Male	229	263	36.8	853	217	33.8
Smoking status						
No smoking history	137	433	60.7	521	482	60.1
Positive smoking history	208	263	36.8	800	217	33.8
Histology						
Adenocarcinoma	266	378	51.8	1,025	358	49.2
Other	89	216	29.7	322	189	28.2
Disease stage						
Metastatic	254	299	41.4	1,055	274	40.8
Nonmetastatic	106	433	58.5	298	435	57.0
Performance status						
0-1	225	433	56.6	932	443	57.2
2	65	204	31.2	270	141	18.7
3-4	70	81	26.7	146	63	10.1
Previous chest surgery						
Yes	131	481	63.6	396	462	57.5
No	224	247	36.7	952	262	39.0

in all patients who received gefitinib after the failure of prior chemotherapy. Given that the present study included many elderly and patients with a poor PS, these survival data do not differ substantially from those obtained with the Japanese cohort of a phase II study (11.8 months and 50%, respectively).[6] These findings suggest that gefitinib treatment in clinical practice may lead to clinical benefit as it did in the clinical trials. Furthermore, the survival data in the present study are similar to those obtained with previously treated patients with a PS of 0 to 2 in a phase III trial of docetaxel (7.5 months and 37%, respectively), which is a standard second-line treatment for NSCLC.[30] These observations emphasize the importance of further comparison of gefitinib with docetaxel as a second-line treatment for NSCLC in ongoing phase III studies. In previous phase III clinical trials, however, gefitinib failed to prolong survival in unselected patients, suggesting

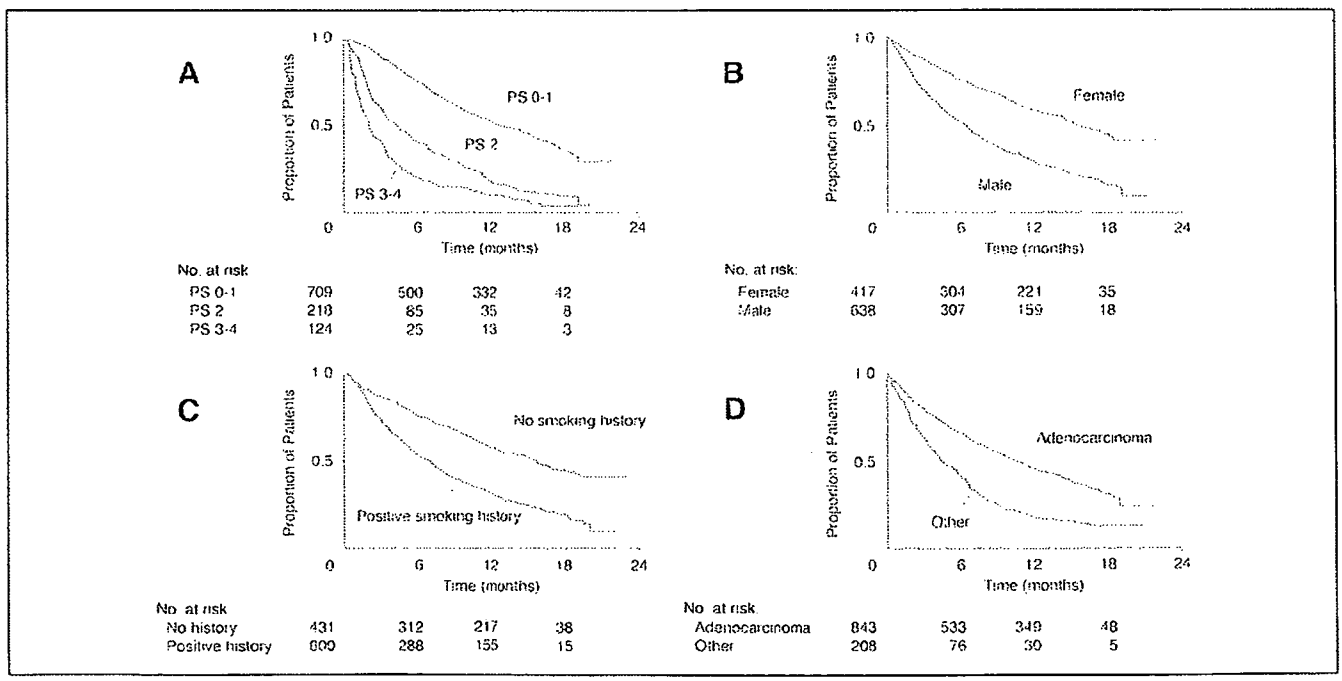

Fig 2. Kaplan-Meier plots of survival for patients with metastatic non-small-cell lung cancer previously treated with chemotherapy classified according to (A) performance status (PS), (B) sex, (C) smoking status, and (D) histology.

the necessity for patient selection on the basis of clinical or genetic factors if true clinical benefit is to be achieved from gefitinib treatment.[19,20,31] Indeed, a randomized phase III trial is now planned in Asian countries to assess the effect of gefitinib on survival in patients selected on the basis of clinical profile.

In conclusion, we have determined the prevalence of gefitinib-related ILD and identified risk factors for this life-threatening adverse event in a large population of Japanese patients with NSCLC treated with this drug. Our data confirmed an acceptable single-agent activity of gefitinib in routine clinical practice. We found that female sex and the absence of a history of smoking, which were known predictive factors for the efficacy of gefitinib, were also associated with a lower risk of gefitinib-induced ILD. Thus, our results indicate that patient selection on the basis of clinical factors can simultaneously minimize the risk of life-threatening ILD and maximize the clinical benefit of gefitinib treatment. They provide both important insight into individual risk-benefit assessment for gefitinib therapy in the practical setting as well as a basis for the planning of future clinical trials to accurately define the scope for gefitinib treatment in NSCLC patients.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Randomized Phase II Study of Carboplatin/Gemcitabine versus Vinorelbine/Gemcitabine in Patients With Advanced Nonsmall Cell Lung Cancer

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BACKGROUND. Combined gemcitabine and carboplatin (GC) and combined gemcitabine and vinorelbine (GV) are active and well tolerated chemotherapeutic regimens for patients with advanced nonsmall cell lung cancer (NSCLC). The authors conducted a randomized Phase II study of GC versus GV to compare them in terms of efficacy and toxicity.

METHODS. One hundred twenty-eight patients with Stage IIIB or IV NSCLC were randomized to receive either carboplatin at an area under the curve of 5 on Day 1 combined with gemcitabine 1000 mg/m^2 on Days 1 and 8 (n = 64 patients) or vinorelbine 25 mg/m^2 combined with gemcitabine 1000 mg/m^2 on Days 1 and 8 (n = 64 patients) every 3 weeks.

RESULTS. Response rates were 20.3% for the GC patients and 21.0% for the GV patients. In the GC arm, the median survival was 432 days, and the a 1-year survival rate was 57.6%; in the GV arm, the median survival was 385 days, and the 1-year survival rate was 53.3% in the GV arm. The median progression-free survival was 165 days in the GC arm and 137 days in the GV arm. Severe hematologic toxicity (Grade 4) was significantly more frequent in the GC arm (45.3% vs. 25.8% in the GV arm; P = .022). Most notably, the incidence of Grade 3 or 4 thrombocytopenia was significantly higher in the GC arm (81.3% vs. 6.5% in the GV arm; P < .001). Conversely, severe nonhematologic toxicity (Grade 3 or 4) was more common in the GV arm (7.8% vs. 19.4% in the GC arm; P = .057).

CONCLUSIONS. Although the GV and GC regimens had different toxicity profiles, there was no significant difference in survival among patients with NSCLC in the current study. *Cancer* **2006;107:599–605.** © *2006 American Cancer Society.*

KEYWORDS: gemcitabine, carboplatin, vinorelbine, nonsmall cell lung cancer.

Unfortunately, nonsmall cell lung cancer (NSCLC) belongs to a group of relatively chemoresistant neoplastic diseases. Recent meta-analyses have shown that cisplatin-based chemotherapy regimens improve survival,[1] and they now are considered standard treatment for patients with NSCLC. Most cisplatin-based regimens have substantial toxicities that require close monitoring and supportive care. Thus, active and less toxic chemotherapeutic regimens that include new, active compounds with novel mechanisms of action need to be developed. The recommendations recently presented in the American Society Clinical Oncology guidelines for chemotherapy in patients with Stage IV NSCLC stated that nonplatinum-containing chemotherapeutic regimens may be used as alternatives to platinum-based regimens as first-line treatment.[2,3]

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Carboplatin, which is an analog of cisplatin, administered either alone or in combination therapy, is associated with less emesis, nephrotoxicity, and neurotoxicity than cisplatin and has been proven to be as effective as cisplatin in NSCLC.[4,5] Several novel chemotherapeutic agents currently are being evaluated for the treatment of patients with advanced NSCLC. The combination of gemcitabine and carboplatin (GC) is a promising carboplatin-containing regimen and has been evaluated in several randomized trials. Mazzanti et al. conducted a randomized Phase II study of GC versus gemcitabine and cisplatin (GP) and observed no differences in activity between the 2 regimens, although there was less emesis, neuropathy, and renal toxicity with GC.[6] The same results were confirmed in a Phase III study of GC versus GP that was conducted by Zatloukal et al.[7] Moreover, GC reportedly prolonged survival significantly compared with single-agent carboplatin in a randomized Phase III study.[8]

The combination of gemcitabine and vinorelbine (GV) is among the representative nonplatinum regimens. GV has demonstrated promising activity and mild toxicity in some Phase II studies. We also conducted a Phase II trial of GV in patients with Stage IIIB and IV NSCLC and observed that toxicity was modest and was managed easily, and overall survival was promising (median survival, 13.9 months).[9] Several randomized Phase III trials have shown that this regimen conferred a comparable survival advantage and was less toxic than standard cisplatin-based chemotherapy.[10,11]

Thus, we can state reasonably that both GC and GV are attractive alternatives to cisplatin-based chemotherapy. However, we have neither survival data nor toxicity data for GC in Japanese patients with NSCLC. Therefore, we conducted a randomized Phase II trial of GC versus GV in patients with advanced NSCLC to compare the efficacy, feasibility, and toxicity profiles of the 2 regimens. The primary endpoint was the 1-year survival rate, and secondary endpoints were overall survival, the time to progression, and the response rate.

MATERIALS AND METHODS

Patient Selection

The patients who were enrolled in this trial had histologically or cytologically confirmed Stage IIIB or IV NSCLC. Patients with Stage IIIB disease who were not candidates for thoracic radiation and patients with Stage IV disease were eligible if they had not received previous chemotherapy, had measurable disease, and had a life expectancy $\geq$3 months. Patients who had received previous radiotherapy were included if they had assessable disease outside of the radiation field. Patients with who had postoperative recurrences also were allowed. Additional entry criteria were age between 20 years and 74 years, a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale, and adequate bone marrow function (leukocyte count $\geq$3500/μL, neutrophil count $\geq$2000/μL, hemoglobin concentration $\geq$10.0 g/dL, platelet count $\geq$ 100,000/μL), kidney function (creatinine $\leq$1.2 mg/dL), liver function (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels $\leq$2.5 times the upper limit of normal; and total bilirubin $\leq$1.5 mg/dL), and pulmonary function (partial pressure of alveolar oxygen $\geq$60 torr). Patients were excluded if they had any active concomitant malignancies, symptomatic brain metastases, prior radiotherapy to the sole site of measurable disease, past history of severe allergic reactions to drugs, interstitial pneumonia identified by chest X-ray, cirrhosis, superior vena cava syndrome, or other serious complications, such as uncontrolled angina pectoris, myocardial infarction within 3 months, heart failure, uncontrolled diabetes mellitus or hypertension, and uncontrolled massive pleural effusion or ascites. All patients gave written informed consent, and the Institutional Review Board for Human Experimentation approved the protocol.

Randomization and Treatment Plan

Patients were assigned randomly to receive the GC regimen or the GV regimen and were stratified by disease stage (Stage IIIB vs. Stage IV), prior treatment (yes vs. no), and institution. On the GC regimen, gemcitabine was given at a dose of 1000 mg/m^2 in 100 mL of normal saline solution as a 30-minute intravenous infusion on Days 1 and 8. Carboplatin was administered at area under the curve (AUC) of 5 in 500 mL of normal saline solution as a 60-minute intravenous infusion on Day 1 only. We used the Calvert formula[12] to determine the dose of carboplatin as follows: dose in mg = target AUC $\times$ (creatinine clearance + 25). The glomerular filtration rate was estimated by using the formula described by Gault et al.[13]

The GV regimen consisted of gemcitabine 1000 mg/m^2 in 100 mL of normal saline solution as a 30-minute intravenous infusion and vinorelbine 25 mg/m^2 in 20 mL of normal saline solution as a 5-minute intravenous infusion on Days 1 and 8. The scheduled Day-8 treatment was delayed until recovery (no longer than 1 week) if patients had a leukocyte count <2000/μL, platelet count <75,000/μL, interstitial pneumonia Grade $\geq$1, constipation Grade $\geq$3, and/or other nonhematologic toxicities Grade $\geq$2. If these parameters did not improve sufficiently, then the Day-8 gemcitabine and vinorelbine doses were omitted.

Both regimens were repeated every 3 weeks. The subsequent course of chemotherapy was begun if patients had a leukocyte count $\geq$3000/μL, neutrophil count $\geq$1500/μL, platelet count $\geq$100,000/μL, creatinine $\leq$1.5 mg/dL, AST and ALT levels $\leq$2.5 times the upper limit of normal, and total bilirubin $\leq$1.5 times the upper limit of normal. A 2-week delay in initiating the subsequent course was allowed. Otherwise, the patient was withdrawn from the study. We planned for patients to receive at least 3 cycles, up to a maximum 6 cycles, of chemotherapy unless there was evidence of disease progression, intolerable toxicity, or patient refusal.

For dose modification in the subsequent cycle in both arms, if, during the previous course, Grade 4 leukopenia, chemotherapy-induced neutropenic fever >38°C, thrombocytopenia (< 20,000/μL), nonhemotologic toxicity Grade $\geq$3, or cancellation of Day-8 treatment had occurred, then the doses of gemcitabine, vinorelbine, and carboplatin were reduced by 200 mg/m^2, 5 mg/m^2, and AUC 1, respectively. Treatment was discontinued in patients who could not tolerate either gemcitabine 800 mg/m^2 and carboplatin AUC 4 or gemcitabine 800 mg/m^2 and vinorelbine 20 mg/m^2.

It was acceptable to administer a 5-hydroxytriptamine receptor antagonist and/or dexamethasone intravenously before the start of chemotherapy to prevent nausea and emesis. The use of granulocyte-colony stimulating factors was not allowed during treatment except in patients who had Grade 4 leukopenia, Grade 4 neutropenia, or febrile neutropenia, according to the investigator's decision. Transfusions of red blood cells and platelets were allowed in patients who had Grade $\geq$3 anemia and in patients who had platelet counts $\leq$20,000/μL and/or a tendency for bleeding.

Treatment Evaluation

Before enrollment in the study, all patients provided a complete medical history and underwent physical examination. We obtained a complete blood count, blood chemistry, blood gas analysis, chest X-ray, electrocardiography, computed tomographic (CT) scans of the brain and chest, a CT scan or ultrasound examination of the abdomen, and a bone scintigram. Patients were monitored weekly throughout treatment by physical examination, recording of toxic effects, complete blood cell counts, and blood chemistry. Studies of drug-related toxicities were evaluated according to National Cancer Institute Common Toxicity Criteria (version 2.0, revised 1994).

Tumor responses were classified according to the Response Evaluation Criteria in Solid Tumors.[14] In target lesions, a complete response (CR) was defined as the complete disappearance of all target lesions for a minimum of 4 weeks, during which no new lesions appeared. A partial response (PR) was defined as a decrease $\geq$30% in the sum of the greatest dimensions of target lesions for a minimum of 4 weeks. Progressive disease (PD) was defined as an increase $\geq$20% in the sum of the greatest dimensions of target lesions or the appearance of $\geq$1 new lesion(s). Stable disease (SD) was defined as neither sufficient shrinkage to qualify for a PR nor a sufficient increase to qualify for PD for a minimum of 6 weeks. Response duration in patients who achieved a CR or PR was measured from the start of treatment to the date of disease progression.

In nontarget lesions, a CR was defined as the disappearance of all nontarget lesions. An incomplete response/SD was defined as the persistence of $\geq$1 nontarget lesion(s). PD was defined as the appearance of $\geq$1 new nontarget lesion(s) and/or unequivocal progression of existing nontarget lesions. An extramural review was conducted to validate staging and responses during a regular meeting of the West Japan Thoracic Oncology Group.

Statistical Methods

The main objective of this study was to test whether either of the 2 regimens had promise in terms of increasing survival. Each arm was to be analyzed separately. One or both of the regimens would be considered promising if the true 1-year survival rates were $\geq$55%, or the regimens would be of no additional interest if the true 1-year survival rates were $\leq$32%. The study was designed to accrue 57 patients to each arm over 12 months followed by 1 additional year of follow-up to confer a power of 0.80 for a 1-sided .05 level for a 1-year survival rate of 32% versus 55%.

We compared Kaplan–Meier curves for overall survival and progression-free survival by using the standard log-rank test. Overall survival was defined as the interval from the date of random treatment assignment to the date of death or last follow-up information for patients who remained alive. Progression-free survival was defined as the interval from the date of random treatment assignment to the date of progression or death, whichever occurred first, or last follow-up information for patients who remained alive and for patients whose disease did not progress.

Patient characteristics except for age, response rates, dose reduction rate in each cycle, and toxicity incidence, were compared by using Pearson chi-square contingency table analysis. Age and the number of treatment cycles were compared by using the Wilcoxon test.

TABLE 1
Baseline Patient Characteristics

Characteristic	No. of patients		P
	GC	GV	
Total no. of patients	64	64	
Gender			.851
Male/female	43/21	42/22	
Age, y			
Median	60	62	.929
Range	30–74	36–74	
PS			
0/1	25/39	24/40	.855
Smoking history			
Yes/no	18/46	27/37	.095
Histology			
Adenocarcinoma	36	45	.128
Squamous cell carcinoma	21	16	
Others	7	3	
Disease stage			
Stage IIIB/IV	16/48	16/48	1.000
Prior treatment			
Yes/no	15/49	14/50	.832

GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine; PS, performance status.

RESULTS

Patient Characteristics

From June 2001 to October 2002, 128 patients were assigned to receive GC ($n = 64$ patients) or GV ($n = 64$ patients). All enrolled patients were eligible. Baseline patient characteristics according to treatment arm are shown in Table 1. Patients essentially were divided equally between the 2 treatment arms in terms of gender, age, performance status, disease stage, and histologic subtypes. Patients with Stage IIIB disease accounted for 27% of the study population, and patients with adenocarcinoma accounted for 63% of the study population. In the GV arm, 2 patients did not receive trial therapy because of deterioration in their condition. These 2 patients were excluded from the analysis of toxicity, response, and progression-free survival.

Treatment Delivery

Median numbers of 3 cycles and 4 cycles were administered in the GC and GV arms, respectively. Three or more cycles were delivered to 76.6% and 72.6% of patients, and 6 cycles were delivered to 7.8% and 32.3% of patients in the GC and GV arms, respectively. Differences between arms in the number of chemotherapy courses administered were not statistically significant ($P = .161$) (Table 2).

Chemotherapy was omitted on Day 8 for 6.4% of patients in the GC arm and for 3.8% of patients in the GV arm. Dose reductions in the second cycle were more frequent in the GC arm than in the GV arm (49.2% vs. 14.8%, respectively; $P < .001$). The dose reduction rates after the second cycle did not differ between the 2 arms (Table 2). Most dose reductions in the GC arm were because of hematologic toxicity, especially thrombocytopenia. Reasons for stopping treatment also differed between the 2 arms; Treatment was stopped before 3 cycles for disease-related causes (progression or death) in 46.7% and 58.8% of patients and because of toxicity or refusal in 40.0% and 29.4% of patients in the GC and GV arms, respectively.

TABLE 2
Treatment Delivery and Dose Reduction Rate

No. of cycles	Gemcitabine and carboplatin		Gemcitabine and vinorelbine	
	No. of patients (%)	No. of patients who required dose reduction (%)	No. of patients (%)	No. of patients requiring dose reduction (%)
2	61 (95.3)	30 (49.2)	54 (87.1)	8 (14.8)
3	49 (76.6)	6 (12.2)	47 (75.8)	6 (13.3)
4	29 (45.3)	2 (6.7)	34 (54.8)	2 (5.9)
5	9 (14.1)	2 (22.2)	24 (38.7)	1 (4.2)
6	5 (7.8)	0	20 (32.2)	0

Treatment Response and Survival

In the GC arm, there was 1 CR and 12 PRs for an overall response rate of 20.3%. In addition, 34 patients (53.1%) had SD, and 17 patients (26.6%) had PD. In the GV arm, there were 2 CRs and 11 PRs for an overall response rate of 21.0%. There were 29 patients (46.8%) with SD and 17 patients (27.4%) with PD. The difference in the overall response rate between the 2 arms was not significant ($P = .60$).

Overall and progression-free survival curves for the 2 treatment arms are shown in Figures 1 and 2. The 1-year survival rate was 57.6% (95% confidence interval, 45.5–69.8%) in the GC arm versus 53.3% (95% confidence interval, 40.8–65.7%) in the GV arm. Respective median survival, 2-year survival rates, and median progression-free survival were 432 days, 38.3%, and 165 days in the GC arm and 385 days, 22.4%, and 137 days in the GV arm. No significant differences were noted between groups in progression-free survival ($P = .676$) or overall survival ($P = .298$), although there were trends toward higher 1-year and 2-year survival rates in the GC arm.

After primary chemotherapy, 94 patients (73.4%) received other chemotherapeutic agents with no difference between the 2 arms (47 patients in the GC arm and 47 patients in the GV arm received other chemotherapeutic agents). In the GC arm, 27 patients

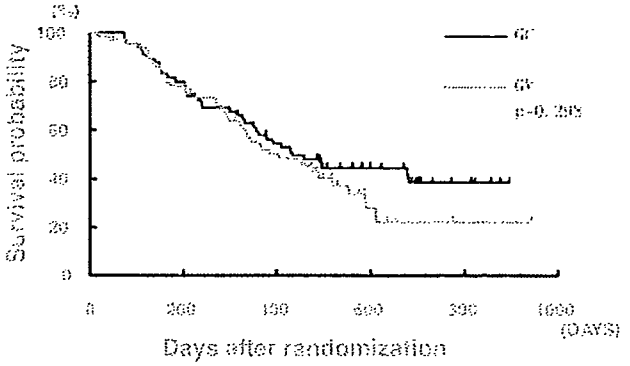

FIGURE 1. Overall survival is illustrated for the 2 treatment arms. GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine.

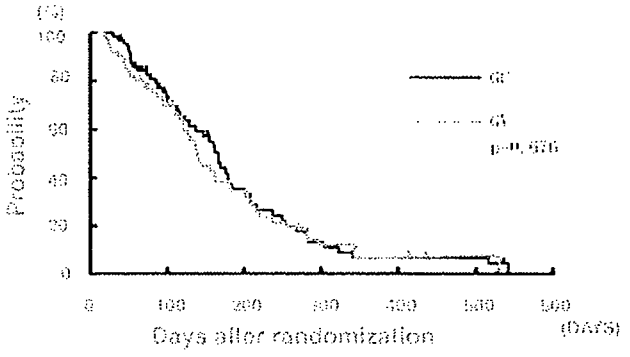

FIGURE 2. Progression-free survival is illustrated for the 2 treatment arms. GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine.

received a single anticancer agent (docetaxel, 17 patients; vinorelbine, 4 patients; gemcitabine, 3 patients; other agents, 3 patients). Platinum doublets were given to 12 patients (carboplatin and paclitaxel, 3 patients; cisplatin and docetaxel, 3 patients; carboplatin and docetaxel, 2 patients; other doublets, 4 patients). In the GV arm, 21 patients received platinum doublets (carboplatin and paclitaxel, 14 patients; carboplatin and docetaxel, 3 patients; other doublets, 4 patients). A single cytotoxic agent was given to 9 patients (docetaxel, 6 patients; vinorelbine, 1 patient; gemcitabine, 1 patient; other agents, 3 patients). There was a tendency for more patients to receive single-agent chemotherapy, whereas fewer patients received platinum doublets, in the GC arm. The number of patients who received gefitinib treatment apparently did not differ between the 2 arms (31 patients in the GC arm and 27 in the GV arm received gefitinib).

Toxicity

Severe hematologic toxicity (Grade 4) was significantly more frequent in the GC arm (45.3% vs. 25.8% in the GV arm; $P = .022$). Conversely, severe nonhematologic toxicity (Grade 3 or 4) occurred more often in the GV arm (7.8% vs. 19.4% in the GC arm; $P = .057$). There were no treatment-related deaths.

TABLE 3
Hematologic Toxicity: Maximum Toxicity Grade in Any Course*

Toxicity	No. of patients (%) GC	GV	P
Leukopenia			
Grade ≥3	34 (53.1)	26 (41.9)	.208
Grade 4	1 (1.6)	1 (1.6)	.981
Neutropenia			
Grade ≥3	51 (79.7)	40 (64.5)	.057
Grade 4	22 (34.4)	16 (25.8)	.294
Anemia			
Grade ≥3	32 (50.0)	3 (4.8)	<.001
Grade 4	9 (14.1)	0	.002
Thrombocytopenia			
Grade ≥3	52 (81.3)	4 (6.5)	<.001
Grade 4	6 (9.4)	0	.013
Platelet transfusion			
Yes	29 (45.3)	0	<.001
Febrile neutropenia	20		
Yes	5 (7.8)	7 (11.3)	.506

GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine.
* Studies of drug-related toxicities were evaluated according to National Cancer Institute Common Toxicity Criteria (version 2.0, revised 1994).

Hematologic and nonhematologic toxicities are listed in Tables 3 and 4. Hematologic toxicity was prominent. In particular, the incidence of Grade 3 or 4 thrombocytopenia was significantly higher in the GC arm (81.3% vs. 6.5% in the GV arm; $P < .001$). However, most patients who had thrombocytopenia in the GC arm did not experience bleeding. Two patients had Grade 3 bleeding in the GC arm. Patients in the GC arm required more platelet transfusions (45.3% vs. 0.0% in the GV arm; $P < .001$). Grade 3 or 4 neutropenia and anemia also occurred in a significantly higher percentage of patients in the GC arm (neutropenia, 79.7% vs. 62.5% in the GV arm; $P < .031$; anemia, 50.0% vs. 4.7% in the GV arm; $P < .001$). The difference in febrile neutropenia incidence was not significant. ($P = .264$).

Nonhematologic toxicity was mild. Grade ≥2 nausea occurred significantly more often in the GC arm than in the GV arm (21.0% vs. 42.2%; $P = .010$). Conversely, Grade ≥2 phlebitis (29.0% vs. 0%; $P < .001$) and hepatic toxicity (elevation of AST or ALT, 43.5% vs. 25.0%; $P = .028$) were significantly more common in the GV arm than in the GC arm. Other nonhematologic toxicities occurred with similar frequency in the 2 treatment arms.

There was 1 treatment-related death in the GV arm, which was caused by pneumonitis. No treatment-related deaths occurred in the GC arm.

TABLE 4
Nonhematologic Toxicity: Maximum Toxicity Grade in Any Course*

Toxicity	No. of patients (%) GC	GV	P
Nausea			
Grade ≥2	27 (42.2)	13 (21.0)	.010
Grade 3	5 (7.8)	0	-
Emesis			
Grade ≥2	8 (12.5)	5 (8.1)	.413
Grade 3	0	0	-
Fatigue			
Grade ≥2	9 (14.1)	15 (24.2)	.147
Grade 3	2 (3.1)	2 (3.2)†	-
Diarrhea			
Grade ≥2	0	2 (3.2)	.147
Grade 3	0	1 (1.6)	-
Constipation			
Grade ≥2	28 (43.8)	19 (30.6)	.128
Grade 3	3 (4.7)	1 (1.6)	-
Rash			
Grade ≥2	11 (17.2)	11 (17.7)	.934
Grade 3	2 (3.1)	1 (1.6)	-
Phlebitis			
Grade ≥2	0	18 (29.0)	<.001
Grade 3	0	0	-
Pneumonitis			
Grade ≥2	0	3 (4.8)	.074
Grade 3	0	2 (3.2)‡	-
ALT/AST			
Grade ≥2	16 (25.0)	27 (43.5)	.028
Grade 3	5 (7.8)	12 (19.4)	.057
Creatinine			
Grade ≥2	0	1 (1.6)	.307
Grade 3	0	1 (1.6)	-

GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
* Studies of drug-related toxicities were evaluated according to National Cancer Institute Common Toxicity Criteria (version 2.0, revised 1994).
† One patient had Grade 3 fatigue, and 1 patient had Grade 4 fatigue.
‡ One patient had Grade 3 pneumonitis, and 1 patient had Grade 5 pneumonitis.

DISCUSSION

This study, the first cooperative group trial to our knowledge of the GC regimen, demonstrated the feasibility of the GC regimen compared with the GV regimen. The GC regimen was identified as a promising regimen for patients with advanced NSCLC. Sederholm et al. of the Swedish Lung Cancer Group demonstrated that GC conferred a significant survival advantage compared with gemcitabine alone.[8] Other Phase III trials demonstrated that the GC regimen was tolerated better; conferred a survival advantage over the combination of mitomycin, ifosfamide, and cisplatin;[15] and resulted in a comparable survival advantage and less nausea and emesis compared with GC.[7]

Based on a large body of Phase II data, including those from our study,[9] and Phase III data, the GV regimen apparently produces less hematologic and nonhematologic toxicity, when it is compared indirectly with more standard combinations. In recent Phase III studies, GV was compared with cisplatin-based regimens. Overall, there was no significant difference in survival, but toxicity was less pronounced.[10,11,16]

GC and GV have comparable efficacy and less toxicity than platinum doublets, as discussed above. However, we do not know which regimen, GC or GV, is more feasible or more effective. Thus, we conducted a randomized study to compare the 2 regimens.

This randomized Phase II study showed that GC and GV are tolerated well and have comparable activity in patients with advanced NSCLC. However, there were marked differences in hematologic toxicity and moderate differences in nonhematologic toxicity. GC resulted in higher incidences of Grade 3 or 4 neutropenia, anemia, and thrombocytopenia. Conversely, hepatic toxicity and phlebitis were increased in patients who received GV.

GC was associated with more thrombocytopenia. The difference in the incidence of severe thrombocytopenia between our study and European or American studies may be attributable to blood counts that were obtained more often in Japan (more than once or twice per week) or to ethnic differences. It is unknown whether there are any the ethnic differences between Japanese and European or American patients concerning thrombocytopenia on the GC regimen. However, a report described severe hematologic toxicity with the combination of paclitaxel and carboplatin that may have been caused by an ethnic difference. Gandara et al. performed a comparative analysis of paclitaxel and carboplatin from cooperative group studies in Japan and the United States. Their analysis showed that the incidence of Grade 4 neutropenia (69% vs. 26%) and Grade 3 or 4 febrile neutropenia (16% vs. 3%) was significantly higher in Japanese patients despite the lower paclitaxel dose.[17]

Overall efficacy was comparable between the GC and GV arms in the current study. There was a trend toward inferior overall survival in the GV arm, but the differences were small numerically, and the study did not have adequate power to detect survival differences. Survival in the current study was better than that reported in other studies of patients with advanced NSCLC. The median progression-free survival in the GC arm in our study was 165 days and was almost equal to that of GC reported by Rudd et al. (5.3 months)[15]; however, overall survival in our study was much longer (432 days vs. 10 months, respectively). Moreover, the proportion of patients who received second-line therapies

in our study was higher (73% vs. 8%).[15] Thus, we believe that better survival in the current study was because a higher proportion of our patients received second-line therapies.

In conclusion, the current results demonstrated that the GC and GV regimens both were active and well tolerated. Although Grade 3 and 4 thrombocytopenia was more frequent in the GC arm, the low incidence of bleeding indicated that thrombocytopenia was not major clinical problem. Thus, we believe that both the GC regimen and the GV regimen are reasonable treatment options for patients with advanced NSCLC.

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Review Article

Recent trends in the treatment of advanced lung cancer

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Lung cancer is one of the major causes of death in many countries because of high rates of smoking, especially in Asian countries. Lung cancer is divided into two major categories based on their biological characteristics and the selection of treatment methods: non-small cell lung cancer (NSCLC; 85%) and small cell lung cancer (15%). Early detection and complete resection are very important in NSCLC, but the cure rate is not very high, except in stage 1A disease. It is extremely important to understand the biology of lung cancer and to introduce more effective treatments in order to improve the survival of NSCLC patients. Numerous clinical trials involving lung cancer patients have led to 'state-of-the-art' treatments for each stage of the disease. Progress in chemotherapy and molecular target based therapy have altered the standard therapy for NSCLC. (*Cancer sci* 2006; 97: 448–452)

Chemotherapy for advanced non-small cell lung cancer

Platinum-based doublets are considered to be the standard treatments for stage IV non-small cell lung cancer (NSCLC).[1,2] Although the majority of regimens contain cisplatin, carboplatin can be used in combination with paclitaxel because numerous phase III data exist on this combination. The question remains, however, as to whether or not we can treat advanced NSCLC patients with a non-platinum-based regimen. To date, the answer would appear to be that platinum-based therapy is superior, although platinum drugs and/or non-platinum doublets could be used to treat elderly and/or frail patients because of their low renal toxicity. Kosmidis, the chairman of the Hellenic Cooperative Oncology Group, reported the results of their randomized controlled trials looking at the combination of paclitaxel/gemcitabine versus carboplatin + gemcitabine in advanced NSCLC. More than 500 patients were accrued, of which 445 were evaluative. There was no difference in response rate, time to progression or median survival. There was slightly more hematological toxicity with carboplatin and gemcitabine, although it was relatively mild with only 28% having grade 3 and 4 neutropenia. There was slightly more neurotoxicity in the paclitaxel and gemcitabine arm, and the difference was statistically significant. Kosmidis concluded that this was enough evidence to show that non-platinum-based chemotherapy is as good as platinum-based chemotherapy.[3] However, no studies have demonstrated the superiority of a non-platinum doublet over a platinum-based doublet.

Several doublets that include new drugs improve survival, but no one regimen is clearly superior to the others.[1,2] We have conducted a four-arm cooperative study (FACS) in advanced NSCLC. The study was designed to demonstrate non-inferiority of three experimental arms: paclitaxel + carboplatin; gemcitabine + cisplatin; and navelbine + cisplatin in comparison with cisplatin + CPT-11 (control arm). One-year survival (59%) was higher than expected in cisplatin + CPT-11. No statistically significant differences in response rate, time to progression (TTP) or overall survival were observed between the reference and experimental regimens. Non-inferiority of the three experimental arms was not demonstrated. The response duration in the cisplatin + CPT-11 arm was relatively longer than in the other three arms. No statistical test was conducted because these data were obtained from selected populations based on response, such that there is no statistical basis for comparison (Ohe Y *et al.*, unpublished data, 2006). In conclusion, all four platinum-based doublets have similar efficacy for advanced NSCLC but with different toxicity profiles. Cisplatin + CPT-11 is still regarded as the reference regimen in Japan.

The chemotherapy outcomes were compared in Japanese and American NSCLC patients accrued to the FACS trial and the SWOG 0003 trial,[4] respectively. The two trials had similar eligibility and evaluation criteria, although the dose of paclitaxel was 200 mg/m^2 in the Japanese trial and 225 mg/m^2 in the SWOG trial. The purpose of the analysis was to demonstrate similarities and differences in patient characteristics and outcomes between the Japanese and USA trials for advanced stage NSCLC treated by the same regimen, to provide a basis for standardization of the study design/process to facilitate interpretation of future trials, and to take the first step toward possible joint NCI-sponsored studies in lung cancer between Japanese and American investigators. This analysis using carboplatin and paclitaxel as the common arm shows great similarities in patient characteristics between the FACS trial and the SWOG 0003 trial. Frequencies of neutropenia and febrile neutropenia were significantly higher in FACS trials although the paclitaxel dose was lower

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in this group. There may be some differences in population-based pharmacogenomics. Grade 3/4 neuropathy, conversely, was more frequent in the SWOG 0003 trial due to differences in the cumulative paclitaxel dose because of the higher absolute dose and higher median numbers of treatment courses. The response rates were exactly the same, but 1 year survival was better in the FACS trial. These results suggest that future joint Japan–USA clinical trials should consider possible pharmacogenomic differences in drug disposition between Japanese and American populations.[5]

Molecular target-based drugs in advanced recurrent NSCLC

Numerous molecular target-based drugs have been introduced for the treatment of NSCLC, but can they replace current therapy? Can they be used as an adjuvant to current therapy? Can they be combined with other chemotherapeutic agents, radiotherapy and/or surgery?

We hypothesize that incorporation of novel molecular target-based therapies into current treatment paradigms will improve outcomes. However, carefully designed clinical trials and translational science will be required to identify subsets of patients who will benefit.

If we are to use them, we must first answer the following critical questions. Is the target required for a response? Whether or not we know a real and correct molecular target is still questionable. Is the presence of the target sufficient for a response, and can we measure the target in a biologically relevant and/or technologically valid way? Does the agent inhibit the proposed target at the dose and schedule used? Is the target a critical driving force for cell growth in the tumor type in question? The answers to these questions are crucial to treatment with molecular target-based drugs.

Various molecular target-based drugs for advanced NSCLC have been evaluated in randomized controlled trials, but the majority, including a matrix metalloprotease inhibitor, a protein kinase C inhibitor and trastsuzumab, have yielded negative results.[6–8] Gefitinib is an orally available selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that exhibits antitumor activity in patients with previously treated advanced NSCLC.

Clinical trial of gefitinib and erlotinib

Four open-label multicenter phase I studies have identified diarrhea, skin rash/acne and nausea as common adverse events.[9,10] Two large-scale, multicenter randomized controlled phase II trials, IDEAL 1 and 2, have demonstrated clinically significant antitumor activity of gefitinib monotherapy, and erlotinib has also shown promising antitumor activity.[11] Neither drug showed any additive and/or synergistic effect when combined with platinum-based chemotherapy as a first-line treatment for NSCLC.[12,13]

On December 17, 2004, AstraZeneca announced the preliminary results of their Iressa Survival Evaluation in Lung Cancer (ISEL) study. The study had accrued 1692 patients with advanced recurrent/refractory NSCLC. Unfortunately, Iressa failed to significantly prolong survival compared with a placebo (HR = 0.89, $P = 0.087$) in the overall patient population or among patients with adenocarcinoma (HR = 0.83, $P = 0.089$), although a tendency toward a survival benefit was observed in the gefitinib group.[14] The less than 10% response rate did not result in an overall prolongation of survival. A retrospective analysis of patients treated with gefitinib in clinical practice showed that tumor response predictors included 'adenocarcinoma', 'no history of smoking', 'women', and 'Japanese'. Survival in the gefitinib group in the ISEL study was significantly higher for non-smokers ($P < 0.01$) and Asians ($P < 0.01$) than in the placebo group. The survival curves of the two treatment groups were the same for non-Asians. The data obtained from the ISEL study were not surprising, although most observers had expected positive overall results.

The results of similar randomized trials of erlotinib (BR21) were presented at the American Society Clinical Oncology (ASCO) meeting in 2004. Erlotinib significantly prolonged survival in patients with advanced, previously treated refractory/recurrent NSCLC.[15] The two studies referred to above differed in several respects. Sample size was larger in the ISEL study than in the BR21 study, and 10% of the patients in the latter study had a performance status (PS) of 3, whereas only PS-2 patients were accrued by the ISEL study. The follow-up period of the ISEL study was also relatively short (4 months). The overall percentage of patients with adenocarcinoma and the percentage of non-smokers was 50% and 20%, respectively, in both studies. Data stratification into Asians and non-Asians was only performed in the ISEL study. The stratified survival data for Asians in the BR21, submitted to the US FDA, showed a tendency that was similar to the stratified data in the ISEL study. The survival of non-smokers in the erlotinib group in the BR21 study was extremely good and contributed to the improvement in overall survival in the erlotinib group. How can we explain the discrepancy of the result from the ISEL and BR21 studies? Part of the explanation is that the dose of gefitinib in the ISEL study was low, while the BR21 study used nearly the maximum tolerated dose. Another hypothesis is that patient populations in the ISEL study were inappropriately selected, for example, subjects with poor prognostic factors. The shapes of the survival curves for the Intact 1 and 2, TALENT and TRIBUTE studies and for the non-Asians in the ISEL study suggest that EGFR-TKI does not prolong the survival of non-Asian patients with NSCLC, with or without prior chemotherapy.[12,13,16,17] The stratified survival data of the Asians in the Intact 1 and 2, TALENT and TRIBUTE studies should be analyzed.

In the SWOG 0023 trial, patients with stage III NSCLC received chemoradiation therapy then three cycles of a single agent, docetaxel, followed by either a placebo or gefitinib as maintenance. This trial was projected to have 80% of the patients receiving either placebo or gefitinib with a drop off of 20% during this part of the therapy. The drop off rate before randomization was a bit larger than the expected rate because of progressive disease or death. Investigators asked the Data Safety Monitoring Committee to look at the data to see if they should actually continue the trial because the results of the ISEL study were negative. This early unplanned analysis showed there was no difference in time to progression in either arm and the P-value for difference was 0.54. Similarly, there was no statistically significant difference in

survival and the *P*-value was 0.09, favoring the placebo group. It was surprising and disappointing that the gefitinib-treated patients were actually experiencing worse survival than the placebo patients. This trial had the power to show a 0.33% advantage for gefitinib and the data were sufficient to state that the likelihood of showing a 33% survival improvement was 0.0015.[18] These data suggested that there is no rationale for using gefitinib in locally advanced NSCLC in the adjuvant setting.

Molecular marker predicting clinical outcome of EGFR-TKI

The activities of epidermal growth factor receptor (EGFR) inhibitors, gefitinib and erlotinib in lung cancer and the correlation of responses to somatic mutations are the focus of translational research performed in 2004 and 2005. This answers the major question; which patients respond and why? We have demonstrated that PC-9 cells with a 15 bp deletion in exon 19 of the EGFR gene are extremely sensitive to EGFR-TKI.[19] In April and May 2004, Paez and Lynch reported that activating mutations in EGFR are present in a subset of NSCLC tumors and that the tumors are highly sensitive to gefitinib and erlotinib.[20,21] EGFR expression levels are not a predictor of response and EGFR amplification may have an impact, but EGFR-TK mutations seem to be better predictors of responsiveness to gefitinib and erlotinib.[22–24] Mutant EGFR are more sensitive to ligand stimulation and are dramatically more sensitive to EGFR-TKIs.[19–21] The incidence of EGFR mutations is reportedly higher in Asians, including Japanese,[25,26] and Mitsudomi has reported cumulative percentages of those with EGFR mutation-positive status in 1104 patients with NSCLC to be 34% among Asians and 8% among non-Asians.[27] Eighty percent of the patients who responded to EGFR-TKI carried an EGFR mutation (non-Asians, 79% [30/35]; Japanese, 81%: [39/48]). Among non-responders, 0% of non-Asians and 21% of Japanese patients carried an EGFR mutation. These data suggest that the presence of an EGFR mutation is a strong predictor of a favorable response to EGFR-TKI. Mutations have been reported to be significantly more frequent in women, in patients with adenocarcinoma, and in never smokers, and these findings are consistent with the clinical predictors of tumor response in patients treated with EGFR-TKI. Mitsudomi recently reported that the del 746–750 mutation might be superior to the L858R mutation for predicting the gefitinib response and those patients with EGFR mutations survived longer after the initiation of gefitinib treatment than those without mutations.

Recently it has been demonstrated that an additional mutation at codon 790 induced resistance to originally sensitive mutant cells.[28,29]

A variety of results were presented at the ASCO 2005 meeting in Orland with regards to molecular analysis of the EGFR gene and protein expression in patients accrued to pivotal studies of EGFR-TKIs.[30] Lynch reported the results of an analytical study using resected specimens and biopsy samples obtained during IDEAL and INTACT studies of gefitinib.[31] Patients with either an EGFR mutation or amplification represented distinct populations. Among cases with mutations, large numbers were female, non-smokers, had adenocarcinoma or bronchioloalveolar carcinoma, were Eastern-Asian and often showed dramatic response rates to gefitinib. Because the number of cases for this analysis was not sufficient, it was impossible to draw any conclusions about the impact of mutation and amplification on survival.

Tsao tried to identify certain relations among the response rate and survival and molecular biological features such as the mutation, protein expression and gene copy numbers in the BR21 study conducted by NCI-Canada clinical trial group, which demonstrated that erlotinib does significantly prolong survival as compared with a placebo. Response rates were higher in patients with EGFR mutations, immunohistochemistry (IHC)-positive tumors and high gene copy numbers, but a statistically significant difference was observed for copy numbers only. Survival benefit was greater in patients who were IHC positive and had high gene copy numbers. However, mutation positive patients did not benefit more than mutation negative patients. From these data, Tsao concluded that mutation analysis is not required for the selection of patients who will receive erlotinib.[32]

There are some controversial data on the relationship between biomarkers and clinical outcome.[33–37] One of the reasons for discrepant data is the validity of techniques including the quality of the samples analyzed. Giaccone conducted a cross validation analysis of EGFR mutations in samples obtained from the Free University (the Netherlands) and the Dana Faber Cancer Institute.[38] The results were discrepant in some samples because of poor quality. Another reason is patient selection because it was impossible to obtain samples from all patients with advanced lung cancer. In the retrospective studies reported to date, only a small proportion of patients have had tumor samples evaluable for each biomarker, making patient selection problematic and prone to the introduction of selection bias. It is therefore extremely important that samples be obtained from all patients in studies evaluating the relationships between clinical outcome and biomarkers such as EGFR expression, amplification and mutation. Of course, the techniques for evaluable biomarkers should be valid. In this regard, the report of Takano is most reliable because they analyzed all the samples from all patients using three techniques: IHC, gene copy number and mutation. There were no problems with patient selection. Because they used surgically resected specimens they were able to obtain adequate specimen amounts. It could be concluded that if the analyses were conducted accurately, EGFR mutational status would be the major predictor of outcome and increased EGFR copy number associated with gefitinib sensitivity would significantly depend on the presence of EGFR mutations.[39] Technical innovations are essential for the reproducible and reliable analysis of samples from advanced disease patients because only small amounts of the specimen could be obtained from inoperable lung cancer patients.

EGFR-TKI seems to be a very promising drug for the treatment of East-Asian patients with NSCLC with and without a history of prior chemotherapy. The response rate has ranged from 20% to 33% clinically, and it was 30% in a prospective phase II trial on 100 previously untreated NSCLC patients. The median survival time of the Japanese population in the IDEAL 1 trial was 13.8 months.[11] To date, no survival

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data from a phase III study of gefitinib and erlotinib in East Asia are available because no phase III study has been conducted. However, a randomized controlled trial comparing gefitinib and docetaxel as a second-line treatment is in progress in Japan. The trial has a non-inferiority design and a definitive conclusion will be difficult to obtain. An erlotinib phase II evaluation has just finished the accrual of patients in Japan, but government approval will require more time.

The frequency of EGFR mutations and response rate are higher in East-Asian populations than in Western countries. A global randomized controlled trial is scheduled for comparison of first-line standard platinum-based chemotherapy versus gefitinib in East Asians, non-smokers versus light smokers, and patients with adenocarcinoma.

Bevacizumab

Vascular endothelial growth factor (VEGF) was originally described as vascular permeability factor. VEGF is involved in the regulation of new vessel growth, promotion of the survival of immature vasculature and binding to one of two receptors such as FLT-1 or KDR.[40]

Bevacizumab is a monoclonal antibody against VEGF. It is 93% human, it recognizes all isoforms of VEGF-A and has a prolonged half life which makes it very convenient to administer on an every 2- or 3-week basis.

The preliminary randomized phase II trial of ECOG using 7.5 mg/kg or 15 mg/kg of bevacizumab every 3 weeks did meet its primary objective of improvement in time to progression on the high dose arm; 7.4 versus 4.2 months. Also, response and survival were numerically better. Problems with hemoptysis or pulmonary hemorrhage occurred in six patients (four squamous cell and two adeno), four of which actually proved to be fatal.[41] Based on these experiences, the ECOG 4599 trial was designed. The primary objective was to compare survival and secondary objectives were to look at the response rate, time to progression and toxicity.

Eligibility criteria included non-squamous cell carcinoma, no history of major hemoptysis and of neither thrombotic nor hemorrhagic disorders, and no central nervous system metastasis. Patients received standard dose carboplatin and paclitaxel with or without high dose bevacizumab 15 mg/kg every 3 weeks. The sample size was calculated to be over 842, providing the investigators with 80% power to detect a 25% improvement in median survival time from the usual 8–10 months. ECOG had two planned interim analyses at 286 and 455 deaths. The study was closed after the second interim analysis. Response rate was significantly higher in the bevacizumab arm (27%) versus the control arm (10%). Progression free survival also favored the bevacizmab arm. Overall survival was highly statistically significant; 12.5 months in the bevacizumab arm and 10.2 months in the control arm. The hazard ratio was 0.77.[42] Hemorrhage was more common in the bevacizumab arm with a 45% incidence compared to less than 1% in the control arm. There were eight treatment-related deaths in the bevacizumab arm and two in the control arm. These data lead to the conclusion that bevacizumab improves survival compared to platinum and paclitaxel in patients with non-squamous NSCLC, although a small increase in severe bleeding can be expected. ECOG considers paclitaxel, carboplatin with bevacizumab to be a standard for the treatment of this NSCLC subgroup. The study group suggested some future plans for combining bevacizumab with chemotherapy, radiotherapy and other targeted agents in neoadjuvant or adjuvant settings. In Europe, a clinical trial of bevacizumab combined with cisplatin + gemcitabine is ongoing. The critical question is whether or not they can obtain reproducible positive data even if the chemotherapy regimen is changed from pacltiaxel + carboplatin to cisplatin + gemcitabine. In Japan, a combination phase I/II study of bevacizumab with 5FU + LV or FOLFOX recently completed the accrual of patients. Combination treatment using bevacizumab with paclitaxel + carboplatin is scheduled. How to manage severe bleeding, even in selected populations, and the extremely high cost of bevacizumab will be major issues.

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Original Article

Results of a Questionnaire Survey for Symptom of Late Complications Caused by Radiotherapy in Breast Conserving Therapy

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Purpose: The present study aimed to determine the prevalence of subjective symptoms of late complications mainly caused by radiotherapy in breast-conserving therapy (BCT), and to identify patients and treatment factors that may predict such complications.

Materials and Methods: A cross-sectional survey was conducted on 247 patients who had had early breast cancer and who were free of recurrence after BCT. Self-administered questionnaires were mailed to the 247 patients. Patient and treatment factors were analyzed.

Results: Responses were received from 193 of the 247 patients. Common perceptions of late complications included shrinking in size (85%), pain (73%), firmness (65%), thickening of the arm (34%), and changes in skin color (19%). However, high-grade toxicity (above Grade 2) was perceived in only 0.52-7.8% of patients. In multivariate models, shrinking in size was associated with age (P=0.020), pain was associated with additional boost irradiation (P=0.015), and firmness was associated with time after surgery (P=0.004).

Conclusions: Late complications as perceived by the patient herself after BCT are common, but tend to be of minimal severity. Most predictive factors are inevitably associated with late complications. However, the boost irradiation may not be indicated for every patient from a QOL perspective.

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Key words: Breast-conserving therapy; Radiotherapy, Late complication

Introduction

Breast-conserving therapy (BCT) for early breast cancer has become a common treatment protocol. Studies of BCT show a relatively low recurrence rate with a high level of patient satisfaction regarding cosmetic outcome[1-4]. However, longer patient survival may result in increased risk for late complications. Symptomatic late complications are negative factors concerning quality of life (QOL)[5,6]. In clinical practice, we usually inform the patient of this possibility and obtain their consent. Although there are numerous reports about late complications after BCT, these reports show only the objective data about complications assessed by physicians or nurses. There is not sufficient data regarding the late complications as perceived by "patients themselves". We need subjective data from patients in clinical practice.

The goals of this study were to determine the prevalence of the symptoms of late complications caused by radiotherapy in BCT, and to determine patient and treatment factors that may predict such complications.

Patients and Methods

A cross-sectional survey was conducted by sending questionnaires to 247 patients who had undergone postoperative radiotherapy at Yamagata University Hospital between 1993 and 2003, who were alive and had not experienced tumor recurrence. This analysis was limited to patients who had undergone BCT. Patients with synchronous bilateral carcinoma of the breast were excluded.

Questionnaires were sent in the mail and patients were requested to reply the questionnaires. The questionnaire was designed to be easily comprehended by Japanese patients and is

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Table 1. Questionnaires of Our Own Composition Using Examples from the LENT/SOMA Scale

This survey asks for your views about your breast at the present time. Answer every question by selecting the answer as indicated.

1. How much pain do you have ?
   ①Not at all
   ②Occasional and minimal
   ③Intermittent and tolerable
   ④Persistent and intense
   ⑤Refractory and excruciating
2. How much firmness do you have ?
   ①Not at all
   ②Barely palpable increased density
   ③Definite increased density and firmness
   ④Very marked density, retraction and fixation
3. How much skin-color-change your operated breast ?
   ①Not at all
   ②< 1 cm^2
   ③1-4 cm^2
   ④> 4 cm^2
4. How much has your operated breast shrunk in size relative to the normal one ?
   ①10-25 %
   ②> 25-40 %
   ③> 40-75 %
   ④Whole breast
5. If you have any other change of your breast, please write it on the following space.

6. How much did your operated-side arm thicken ?
   ①2 cm-4 cm increase
   ②> 4 cm-6 cm increase
   ③> 6 cm increase
   ④Useless arm
7. If you have had any treatment for problems of your breast such as pain or arm thickening, please write it in the following space.

shown in Table 1. The late effects of normal tissue-subjective, objective, management, and analytic (LENT/SOMA) scale[7] was used as part a reference when designing the questionnaires. The LENT/SOMA scale was translated to in Japanese by ourselves and modified. Thus, our questionnaire was not validated. The terms of "atrophy", "fibrosis", "telangiectasia" and "lymphedema" in the LENT/SOMA scale were translated to "shrinking in size", "firmness", "skin-color change" and "thickening of the arm" respectively, because these technical terms are not to be easily comprehended by patients. Patients were required to make an approximately equal choice between normal and Grade 1-4 toxicity according to perception. The definition of degree of toxicity in our questionnaire was equal to that in the LENT/SOMA scale. During the initial phase of this study, the question for "shrinking in size" was not included, as we had thought that atrophy and/or retraction was predominantly influenced by surgery rather than radiotherapy. Questionnaires including the degree of atrophy and/or retraction were thus sent to only 140 of the 247 patients.

Univariate analysis was performed using the chi-square test to determine correlations between response variables (pain, firmness, shrinking in size, thickening of the arm, and changes in skin color) and predictor variables (age, type of surgery, time after surgery, additional boost radiotherapy, supraclavicular regional radiotherapy, parasternal regional radiotherapy, systemic chemotherapy, T stage). To evaluate interactions and independent influences on factors, multiple logistic regression models were created.

Results

Responses were received from 193 of 247 patients (78%). Medical records of these 193 women were reviewed. The mean age of the 193 patients was 50 years (range, 27-77 years). The median time after surgery was 3.8 years (range, 0.67-11 years). Surgical treatment included quadrantectomy (n=138) and wide resection (n=45). The type of surgery was unknown in 10 patients. Surgical evaluation of axillary lymph nodes was performed in 176 patients (91%), not performed in 6 (3%), and unknown in 11 (6%). Although details of the extent of axillary dissection were unavailable, lower axillary lymph node dissection of Levels I and II was used most often.

After surgery, the breast was treated with tangential fields using 4-MV photons to 50 Gy over 5 weeks in most cases (median dose, 50 Gy; mean, 50 Gy; range, 45-54 Gy). Radiotherapy planning was done using an X-ray simulator. Both fields were treated daily with compensating wedge-filters and no bolus. The primary tumor bed was boosted for patients with close or positive surgical margins (n=25). Boost dose was 10 Gy in most cases (median dose, 10 Gy; mean, 10 Gy; range, 10-16 Gy). Patients with >4 positive axillary lymph nodes (n=12) were treated using an anterior supraclavicular field at a depth of 3-4 cm to a dose of 50 Gy. Patients with tumor of the internal portion of

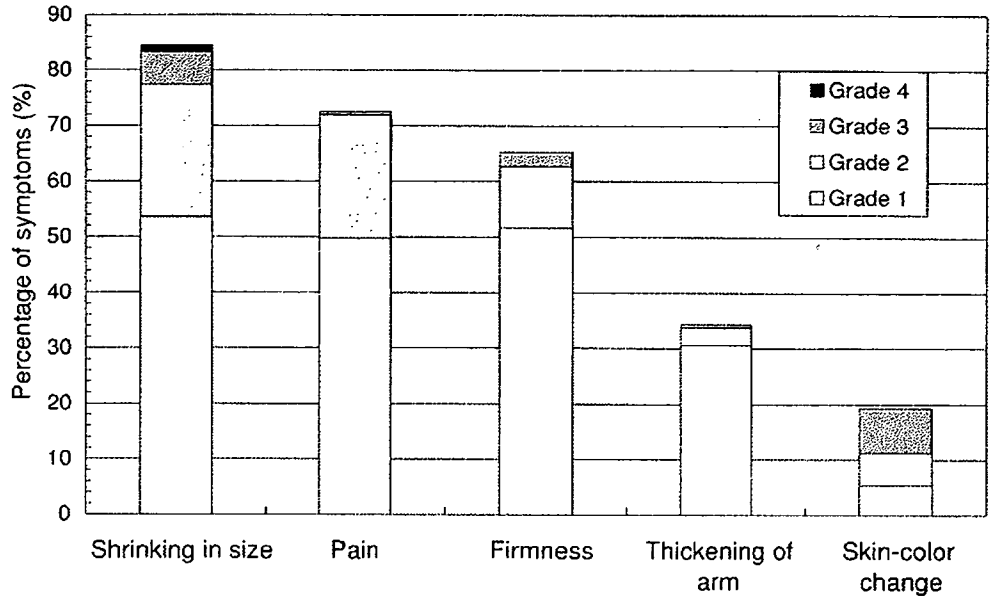

Fig 1. Frequency of reported symptoms based on the LENT/SOMA scale.

breast treated before 1998 (n=9) underwent radiotherapy with an anterior parasternal field to a dose of 50 Gy.

Of the 193 patients, 25 (13%) received chemotherapy. Among patients who received chemotherapy, 2 received cyclophosphamide, 5-fluorouracil, and methotrexate (CMF), 4 received cyclophosphamide, 5-fluorouracil, and epirubicin (CEF), 1 received CEF followed by paclitaxel, 1 received CMF followed by doxifluridine, and 17 patients received 5-fluorouracil or one of its derivatives.

The results of the questionnaire survey of 193 patients are shown in Figure 1. No women were managed using medical or surgical intervention.

Significant predictor variables for development of symptoms over Grade 1 are shown in Table 2. In univariate analysis, shrinking in size was associated with age (P=0.043). Pain was associated with additional boost irradiation (P=0.040). Firmness was associated with time after surgery (P=0.006). Thickening of the arm was associated with systemic chemotherapy (P=0.047), irradiation of the supraclavicular region (P=0.005) and parasternal region (P=0.023). However, in multivariate models, systemic chemotherapy, and irradiation of the supraclavicular and parasternal region were not significantly associated with thickening of the arm.

Discussions

This study used self-administered questionnaires by mail and no physical assessment was done by physician or nurses. It is clear that objective assessment is necessary for scientific estimation. However, in clinical management, patients need information on subjective complications. We believe that not only objective but also subjective assessment is important for patients, because the same grade complications may be perceived by respective patients in several grades.

"Shrinking in size" (atrophy) appears to display a clear association with the volume of resection relative to the volume of the whole breast. Our study revealed that older patients perceived more frequent shrinking in size of the breast, suggesting that older patients have a relatively smaller volume of breast tissue than younger patients. However, in our study, the type of surgery and T stage were not significantly predictive of breast shrinking. Although these results may be influenced by more detailed differences in methods of excision or reconstruction, no clear explanations were apparent from the present study.

Radiotherapy increases the number of patients troubled by breast pain[10]. Breast-specific pain represents an important factor in QOL outcomes for

Table 2. Significant Predictor Variables for Development of Symptoms over Grade 1

	Age (years old) [< 46 vs. 46-60 vs. > 60]	Type of surgery [Bp vs. Bq]	Time after surgery (years) [< 2 vs. 2-5 vs. > 5]	Additonal boost irradiation [No vs. Yes]	Systemic chemotherapy [No vs. Yes]	Irradiation of Supraclavicular region [No vs. Yes]	Irradiation of Parasternal region [No vs. Yes]	T stage [0-1 vs. 2-4]
Shrinking in size	P=0.043 1.000 vs. 2.391 (0.721 - 7.933) vs. 5.000 (1.363 - 18.348)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	P=0.02 1.000 vs. 4.472 (1.025 - 19.507) vs. 6.281 (1.228 - 32.135)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Pain	n.s.	n.s.	n.s.	P=0.040 1.000 vs. 2.627 (1.085 - 6.361)	n.s.	n.s.	n.s.	n.s.
	n.s.	n.s.	n.s.	P=0.015 1.000 vs. 3.302 (1.256 - 8.657)	n.s.	n.s.	n.s.	n.s.
Firmness	n.s.	n.s.	P=0.006 1.000 vs. 0.538 (0.209 - 1.385) vs. 0.100 (0.020 - 0.494)	n.s.	n.s.	n.s.	n.s.	n.s.
	n.s.	n.s.	P=0.004 1.000 vs. 0.296 (0.090 - 0.971) vs. 0.063 (0.005 - 0.834)	n.s.	n.s.	n.s.	n.s.	n.s.
Thickning of arm	n.s.	n.s.	n.s.	n.s.	P=0.047 1.000 vs. 5.643 (1.180 - 26.978)	P=0.005 1.000 vs. 16.031 (3.059 - 84.006)	P=0.023 1.000 vs. 13.920 (2.155 - 89.895)	n.s.
	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Skin-color change	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

In each colomn, p value and odds ratio of univariate analysis are shown at upper stand, and that of multivariate analysis are shown at lower stand.
The value in parentheses represent 95% confidence interval. n.s; not significant.

patients, overriding treatment-related cosmetic status as a predictor of QOL[9]. In our study, although the majority of pain was occasional or minimal, many patients with BCT reported breast pain. In addition, additional boost irradiation was indicated as a predictive factor for breast pain. Additional boost irradiation reduces the risk of local recurrence, particularly in young patients [11]. However, from a QOL perspective, we believe that boost irradiation is not indicated for all patients. Although no clear explanation is apparent for the increase in breast pain with boost irradiation, a number of factors such as fibrosis and atrophy may be responsible.

"Firmness" (fibrosis) is a well-known adverse effect of irradiation, and a dose-effect relationship is a well-established phenomenon[12, 13]. Our patients receiving doses of 50 Gy with or without

10 Gy additional boost irradiation displayed few severe complications, indicating that this dosage is safe. The degree of fibrosis, in our study, tended to be mild in patients a long time after surgery. It suggests that the fibrosis tends to gradually regress.

"Thickening of the arm" (lymphedema) represents an important consideration for QOL, even many years after patients undergo BCT and radiotherapy[6]. The risk of lymphedema of the arm is very low after limited axillary dissection alone or radiotherapy alone[14]. If radiotherapy is added after axillary dissection, the risk of edema is related to the extent of axillary surgery and the radiotherapeutic techniques used[1, 15, 16]. In our study, systemic chemotherapy, irradiation of the supraclavicular region and parasternal region were associated with thickening of the arm in univariate analysis. However, in multivariate models, no predictive factors were associated with thickening of the arm. These results suggest that many factors are associated with thickening of arm and interact with one another. In addition, the extent of axillary surgery may be influential, but was not included as a predictive variable in our study.

Our results suggest that some patients suffer from relatively severe changes in skin color. Although skin-color change includes not only telangiectasia but also pigmentation, our study had no way to distinguish the two based on the questionnaire. However, our own clinical impression suggests that most skin-color change indicates pigmentation.

In conclusion, our study revealed that late complications after BCT are commonly perceived by patients, but tend to be minimal in severity. Most predictive factors are inevitably associated with late complications. However, boost irradiation may be not indicated for every patient from a QOL perspective.

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