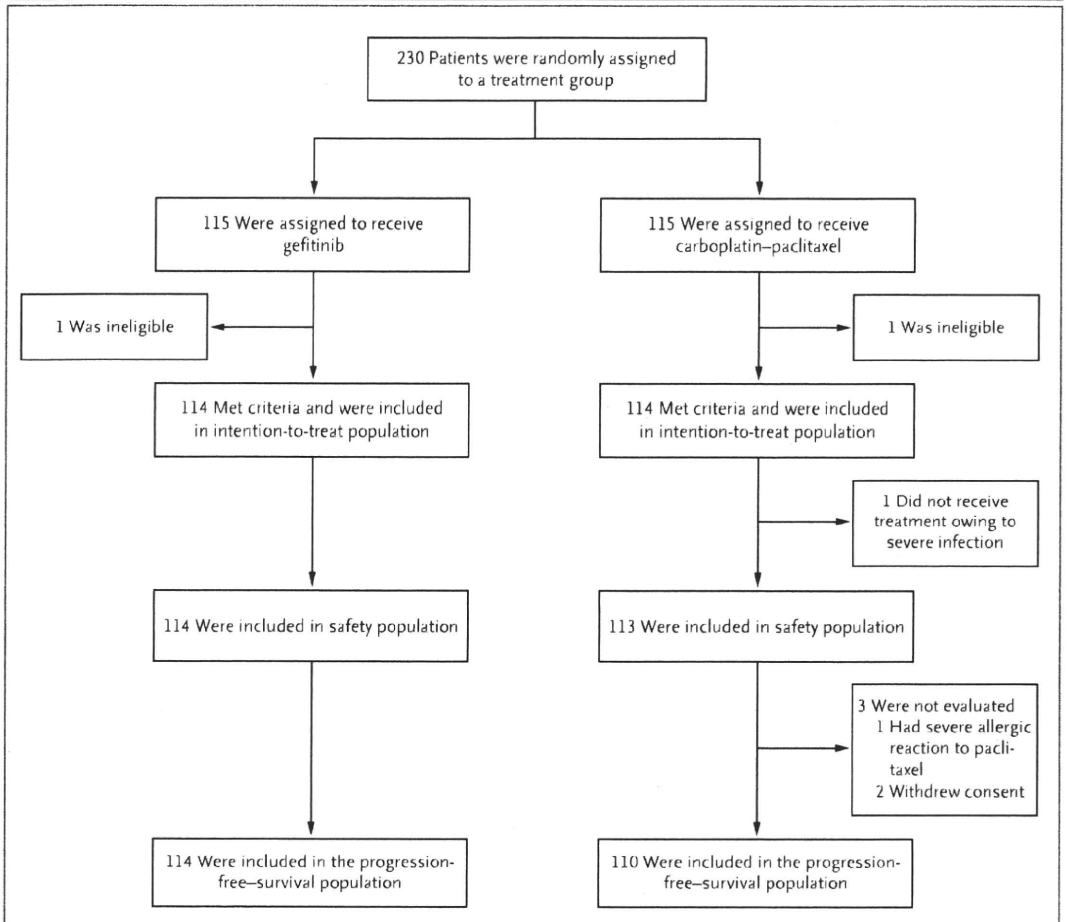

Figure 1. Randomization and Follow-up of the Study Patients, According to Treatment Group.

At the data cutoff point (early December 2009), the median follow-up period was 527 days (>17 months; range, 30 to 1261). The median duration of gefitinib treatment was 308 days (range, 14 to 1219); the median number of 3-week cycles of chemotherapy was 4 (range, 1 to 7). Three patients in the gefitinib group and 11 patients in the chemotherapy group received second-line treatment before they had RECIST-defined disease progression. The data on progression-free survival for these patients were censored at the time of the last CT evaluation at which they did not yet have evidence of disease progression. Demographic and disease characteristics at baseline were well balanced between the two groups (Table 1).

EFFICACY

The interim analysis performed in May 2009 showed that progression-free survival was significantly longer in the gefitinib group than in the chemotherapy group (median, 10.4 months vs. 5.5 months; hazard ratio for death or disease progression with gefitinib, 0.36; 95% confidence interval [CI], 0.25 to 0.51; P<0.001) (Fig. 1 in the Supplementary Appendix). A significant difference was again observed in the final analysis, performed in December 2009 (median progression-free survival, 10.8 months with gefitinib vs. 5.4 months with chemotherapy; hazard ratio, 0.30; 95% CI, 0.22 to 0.41; P<0.001) (Fig. 2A). The 1-year and 2-year rates of progression-free survival were 42.1% and 8.4%, respectively, in the gefitinib group and 3.2% and 0%, respectively, in the chemotherapy group. Subgroup analyses showed that women had significantly longer progression-free survival than men (median, 6.5 vs. 6.0 months; hazard ratio for death or disease progression, 0.68; 95% CI, 0.51 to 0.92; P=0.01). The objective response rate was significantly higher in the gefitinib group than the chemotherapy group (73.7% vs. 30.7%,

Table 1. Baseline Characteristics of the Intention-to-Treat Population, According to Treatment Group.*

Characteristic	Gefitinib (N=114)	Carboplatin–Paclitaxel (N=114)
Sex — no. (%)		
Male	42 (36.8)	41 (36.0)
Female	72 (63.2)	73 (64.0)
Age — yr		
Mean	63.9±7.7	62.6±8.9
Range	43–75	35–75
Smoking status — no. (%)		
Never smoked	75 (65.8)	66 (57.9)
Previous or current smoker	39 (34.2)	48 (42.1)
ECOG performance status score — no. (%)		
0	54 (47.4)	57 (50.0)
1	59 (51.8)	55 (48.2)
2	1 (0.9)	2 (1.8)
Histologic diagnosis — no. (%)		
Adenocarcinoma	103 (90.4)	110 (96.5)
Large-cell carcinoma	1 (0.9)	0
Adenosquamous carcinoma	2 (1.8)	1 (0.9)
Squamous-cell carcinoma	3 (2.6)	2 (1.8)
Other	5 (4.4)	1 (0.9)
Clinical stage — no. (%)		
IIIB	15 (13.2)	21 (18.4)
IV	88 (77.2)	84 (73.7)
Postoperative relapse	11 (9.6)	9 (7.9)
Type of EGFR mutation — no. (%)		
Exon 19 deletion	58 (50.9)	59 (51.8)
L858R	49 (43.0)	48 (42.1)
Other	7 (6.1)	7 (6.1)

* Plus–minus values are means ±SD. ECOG denotes Eastern Cooperative Oncology Group.

P<0.001) (Table 2). The median progression-free survival and response rate did not differ significantly between patients with the EGFR mutation consisting of an exon 19 deletion (11.5 months and 82.8%) and those with the L858R point mutation (in which leucine at amino acid 858 is replaced by arginine) (10.8 months and 67.3%) (Fig. 2B).

The overall survival did not differ significantly between the two treatment groups. The median survival time and the 2-year survival rate were 30.5 months and 61.4% for the gefitinib group, as compared with 23.6 months and 46.7%, respectively, for the carboplatin–paclitaxel group (P=0.31) (Fig. 2C). Neither sex nor clinical stage had a significant effect on overall survival. The time to an ECOG performance status score of 3 or more did not differ significantly between the two groups.

SAFETY

All patients who had received at least one dose of a study drug were included in the safety analysis. The most common adverse events in the gefitinib group were rash and elevated levels of aspartate aminotransferase or alanine aminotransferase, and in the chemotherapy group, appetite loss, neutropenia, anemia, and sensory neuropathy (Table 3, and Table 3 in the Supplementary Appendix). Interstitial lung disease was reported in six patients (5.3%) in the gefitinib group; three cases were severe, and one of the three was fatal. One grade 4 seizure in the gefitinib group and one grade 4 cerebral infarction and one grade 4 bowel obstruction in the chemotherapy group were observed. The incidence of severe toxic effects (NCI-CTC grade ≥3) was significantly higher in the chemotherapy group than in the gefitinib group (71.7% vs. 41.2%, P<0.001).

TREATMENT AFTER PROTOCOL DISCONTINUATION

Data on treatment given after the study protocol was discontinued were collected retrospectively. Though any treatment was permitted, the protocol recommended that the crossover regimen be used as second-line treatment. As of the data cutoff point, 37 patients in the gefitinib group had continued their first-line gefitinib therapy. Among the remaining 77 patients in the gefitinb group who had stopped receiving gefitinib, 52 (67.5%) were receiving carboplatin–paclitaxel as second-line treatment, with a response rate of 28.8%. Sixteen other patients in the gefitinib group were receiving other therapies such as carboplatin–gemcitabine. Among the 112 patients who had completed first-line carboplatin–paclitaxel, 106 patients (94.6%) received second-line gefitinib; 58.5% of these patients had a response.

DISCUSSION

Previous phase 2 studies have suggested that EGFR tyrosine kinase inhibitors are highly effective against mutated-EGFR non–small-cell lung cancer. The current phase 3, prospective, randomized study showed that the use of gefitinib results in progression-free survival that is twice as long

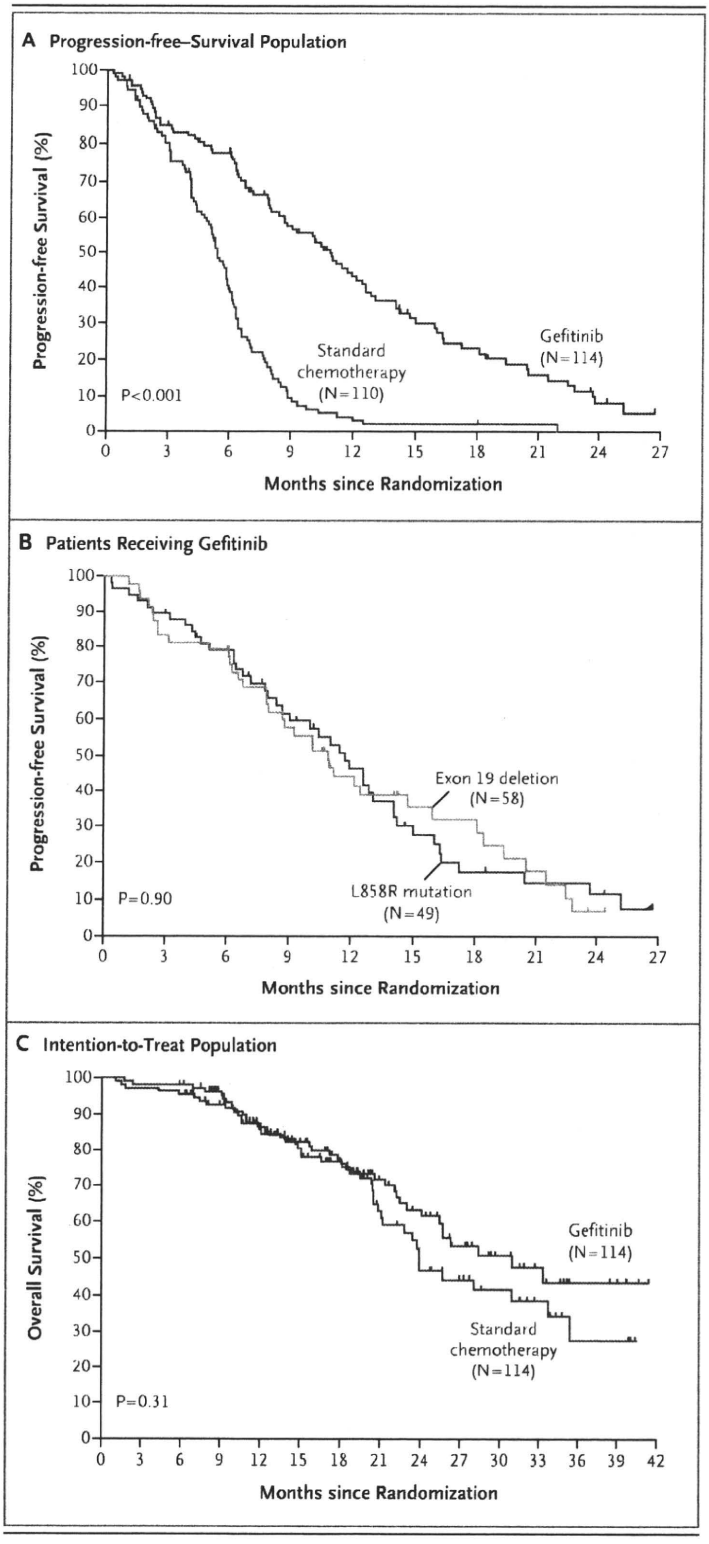

Figure 2. Progression-free Survival and Overall Survival among the Study Patients.

Kaplan–Meier curves for progression-free survival are shown for the progression-free–survival population (Panel A) and for the 107 patients in the gefitinib group with either of the two most common types of epidermal growth factor receptor (EGFR) mutation (Panel B). Kaplan–Meier curves for overall survival in the intention-to-treat population are shown in Panel C. In Panels B and C, tick marks indicate patients for whom data were censored at the data cutoff point (early December 2009).

as that obtained with the use of carboplatin–paclitaxel in patients with mutated-EGFR non–small-cell lung cancer, with a tolerable toxicity profile, including less hematologic toxicity and neurotoxicity than is seen with chemotherapy.

The IPASS, which was conducted in Asia, compared gefitinib with carboplatin–paclitaxel as the first-line treatment for advanced non–small-cell lung cancer in patients selected on the basis of clinical characteristics that included a history of no smoking or light smoking as well as histologic evidence of adenocarcinoma.[7] Although IPASS showed the overall superiority of gefitinib (rate of 1-year progression-free survival, 24.9%, vs. 6.7% with chemotherapy; hazard ratio for death or disease progression, 0.74; P<0.001), the most impressive result emerged from subgroup analysis: as compared with chemotherapy, gefitinib was effective in patients with mutant EGFR (hazard ratio for death or disease progression, 0.48) but was ineffective in those with wild-type EGFR (hazard ratio, 2.85). This finding suggested that the presence of EGFR mutations is the best criterion for selection of patients who benefit from gefitinib, an idea that is validated by the present study.[20] Recently, another Japanese phase 3 study (WJTOG3405; University Hospital Medical Information Network Clinical Trials Registry [UMIN-CTR] number, UMIN000000539) compared gefitinib to cisplatin–docetaxel as the first-line treatment for advanced non–small-cell lung cancer with EGFR mutations.[21] Although this study also showed the superiority of gefitinib over standard chemotherapy with respect to progression-free survival, the magnitude of the benefit was somewhat smaller than in our study, possibly because of differences in the characteristics of the patients (since 41% of patients in WJTOG3405 had had surgery, vs. only 9% in our study) and the duration of follow-up (median, 81 days in WJTOG3405 vs. 527 days in our study).

The standard end point of phase 3 trials of treatments for advanced non–small-cell lung cancer has been overall survival. However, when our trial was begun in 2006, we had data only on

Table 2. Response to Treatment in the Intention-to-Treat Population, According to Treatment Group.*

Response	Gefitinib (N=114)	Carboplatin–Paclitaxel (N=114)
	number of patients (percent)	
Complete response	5 (4.4)	0
Partial response	79 (69.3)	35 (30.7)
Complete or partial response†	84 (73.7)	35 (30.7)
Stable disease	18 (15.8)	56 (49.1)
Progressive disease	11 (9.6)	16 (14.0)
Response that could not be evaluated	1 (0.9)	7 (6.1)

* All responses differed significantly between the two groups ($P<0.001$ by Fisher's exact test).

† The percentage of patients in whom there was either a complete or a partial response was considered to be the rate of objective response.

progression-free survival from our phase 2 studies in patients with non–small-cell lung cancer and EGFR mutations. The data on overall survival first became available in 2008, when the combined analysis of Japanese phase 2 studies (Iressa — Combined Analysis of Mutation Positives [I-CAMP]) and the subgroup analyses of IPASS were reported.[7,22] We thus planned to have progression-free survival as the primary end point in the current study, because it allowed us to calculate the statistical power of the study.

Several studies have suggested that the EGFR copy number may be a better predictive biomarker for the efficacy of EGFR tyrosine kinase inhibitors than the presence of an EGFR mutation.[23] However, its predictive capacity has been reported only in placebo-controlled trials (Iressa Survival Evaluation in Lung Cancer [ISEL][24] and the BR.21 study[23]). Moreover, the subgroup analysis in IPASS showed that longer progression-free survival was significantly associated with sensitive EGFR mutations but not with a high EGFR copy number. We therefore believe that evaluation of the copy number is not necessary when an EGFR mutation test is available. In the current study, EGFR mutations were detected with the use of the PNA-LNA PCR clamp method, the usefulness of which has been validated.[15,16] With this method, EGFR mutations can be detected from small cytologic specimens, such as those from bronchial washings, pleural effusions, and sputum collection, which are frequently used for the diagnosis of advanced non–small-cell lung cancer. The results of the analyses are obtained within several days, so the treatment is usually not delayed. The PNA-LNA PCR clamp approach is readily available and is covered by health insurance in Japan.

The best timing of treatment with an EGFR tyrosine kinase inhibitor for patients with EGFR mutations remains undetermined. A recent study showed that overall survival did not differ significantly between first-line and second-line treatments with erlotinib.[25] Overall survival is considered to be influenced by the second-line or later treatment. In the current study, 95% of the patients in whom first-line carboplatin–paclitaxel failed crossed over to gefitinib therapy. Such a high crossover rate has not been reported in previous studies of EGFR tyrosine kinase inhibitors. For example, in IPASS, only 39% of patients in the first-line chemotherapy group later received an EGFR-tyrosine kinase inhibitor. Considering that in our study the median overall survival in the gefitinib group was 7 months longer than that in the chemotherapy group (30.5 months vs. 23.6 months), in which virtually all patients were given gefitinib as the second-line treatment, and that the rate of response to gefitinib was slightly worse in the second-line setting than in the first-line setting (58.5% vs. 73.7%), first-line gefitinib may be more effective than gefitinib as second-line or later therapy. This idea needs to be tested in studies with large samples or in a meta-analysis.

We believe that the prolonged progression-free survival provided by the use of first-line gefitinib is valuable for patients with advanced non–small-cell lung cancer, who have a poor prognosis. If gefitinib is administered as second-line or third-line treatment, patients may miss the opportunity to receive treatment with gefitinib because of rapidly progressive disease during or after first-line treatment. We believe that the current study, in combination with our previous study of patients with mutated-EGFR non–small-cell lung cancer and poor performance status,[26] establishes the clinical benefit of an EGFR tyrosine kinase inhibitor as first-line treatment in patients with non–small-cell lung cancer and sensitive EGFR mutations.

Predictable toxicity profiles were observed with gefitinib and with carboplatin–paclitaxel in the current study. Diarrhea and rash were seen more often in the gefitinib group, whereas hematologic and neurologic toxic effects were more common in the chemotherapy group. Gefitinib appears to

Table 3. Common Toxic Effects in the Safety Population, According to Treatment Group.*

Toxic Effect	Gefitinib (N=114)					Carboplatin–Paclitaxel (N=113)					P Value for Grade ≥3
	Grade 1	Grade 2	Grade 3	Grade 4	Grade ≥3	Grade 1	Grade 2	Grade 3	Grade 4	Grade ≥3	
	no. of patients				*no. (%)*	*no. of patients*				*no. (%)*	
Diarrhea	32	6	1	0	1 (0.9)	7	0	0	0	0	<0.001
Appetite loss	7	4	6	0	6 (5.3)	39	18	7	0	7 (6.2)	<0.001
Fatigue	8	1	3	0	3 (2.6)	19	11	1	0	1 (0.9)	0.002
Rash	38	37	6	0	6 (5.3)	8	14	3	0	3 (2.7)	<0.001
Neuropathy (sensory)	0	1	0	0	0	28	27	7	0	7 (6.2)	<0.001
Arthralgia	1	2	1	0	1 (0.9)	25	21	8	0	8 (7.1)	<0.001
Pneumonitis	3	0	2	1†	3 (2.6)	0	0	0	0	0	0.02
Aminotransferase elevation	20	13	29	1	30 (26.3)	31	5	0	1	1 (0.9)	<0.001
Neutropenia	5	1	0	1	1 (0.9)	4	9	37	37	74 (65.5)	<0.001
Anemia	19	2	0	0	0	35	32	6	0	6 (5.3)	<0.001
Thrombocytopenia	8	0	0	0	0	25	3	3	1	4 (3.5)	<0.001
Any	17	44	43	4†	47 (41.2)	4	25	41	40	81 (71.7)	<0.001

* Toxic-effect grades are based on the National Cancer Institute Common Terminology Criteria (version 3.0).
† One patient counted here had a grade 5 toxic effect.

be less toxic than carboplatin–paclitaxel. The only exception was interstitial lung disease; there were three cases of severe interstitial lung disease (≥grade 3) in the gefitinib group and none in the chemotherapy group; one of the cases was fatal. The patient who died was a woman who had no history of smoking and thus had a relatively low risk of interstitial lung disease. Gefitinib sometimes causes diffuse alveolar or interstitial damage, especially during the first 3 months of treatment.[27] The estimated incidence of interstitial lung disease is low in many countries (e.g., 0.3% in United States)[28] but is relatively high (4 to 6%) in Japan.[29,30] Every patient treated with an EGFR tyrosine kinase inhibitor should be carefully monitored for this toxic effect.

In conclusion, the efficacy of first-line gefitinib was superior to that of standard chemotherapy, with acceptable toxicity, in patients with advanced non–small-cell lung cancer harboring sensitive EGFR mutations. Selection of patients on the basis of EGFR-mutation status is strongly recommended.

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APPENDIX

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original article

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Randomized phase II trial of weekly paclitaxel combined with carboplatin versus standard paclitaxel combined with carboplatin for elderly patients with advanced non-small-cell lung cancer

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Background: The optimal platinum doublet regimen in elderly patients with non-small-cell lung cancer (NSCLC) is still uncertain. We conducted a randomized phase II study to compare the efficacy and safety of weekly paclitaxel combined with carboplatin with those of the standard schedule.

Patients and methods: Elderly patients (age ≥70 years) with advanced NSCLC were randomly assigned to either the weekly arm {70 mg/m^2 paclitaxel on days 1, 8, and 15 and carboplatin [area under the curve (AUC) = 6] on day 1} or the standard arm [200 mg/m^2 paclitaxel and carboplatin (AUC = 6) on day 1]. The primary end point was the overall response rate (ORR).

Results: Eighty-two patients were enrolled. The ORR and median progression-free survival were 55% and 6.0 months for the weekly arm and 53% and 5.6 months for the standard arm. Grade 3/4 neutropenia and peripheral neuropathy were observed in 41% and 0% of the patients in the weekly arm and in 88% and 25% in the standard arm, respectively.

Conclusions: This is the first randomized study that compares the platinum doublet designed specifically for the elderly. Regarding the safety, the weekly regimen was less toxic than the standard regimen and seems to be preferable for elderly patients with advanced NSCLC.

Key words: elderly patients, non-small-cell lung cancer, weekly paclitaxel

introduction

Lung cancer is the leading cause of cancer deaths in most of the developed countries. More than 80% of the patients with lung cancer have non-small-cell histology and ~40% of the patients present at stage IIIB or stage IV of the disease at diagnosis [1, 2]. For these patients with advanced non-small-cell lung cancer (NSCLC), platinum-based combinations have been accepted as the standard of care on the basis of their survival benefit [3–5]. In particular, the combination of carboplatin and paclitaxel is the most commonly used regimen for the treatment of advanced NSCLC and has been selected as the reference arm in several phase III trials [6, 7]. With regard to the carboplatin and paclitaxel combination, peripheral neuropathy, myalgia, arthralgia, and myelosuppression are the major clinical conditions that distress patients and sometimes lead to treatment withdrawal. To minimize the occurrence of these toxic effects and to improve the tolerability of this regimen, weekly schedule of paclitaxel has been evaluated and found to be associated with a reduction in the treatment toxicity and feasible therapeutic indices for patients with advanced NSCLC although these studies mainly included younger patients and the benefit of such a regimen for elderly patients remains unknown [8–10].

The benefit of platinum doublet chemotherapy for the elderly is still controversial. Some investigators recommend single-agent chemotherapy with new-generation chemotherapeutic agents such as vinorelbine or gemcitabine on the basis of the evidences from some phase III trials [11–13]; on the other hand, others consider that platinum doublet chemotherapy is also acceptable for elderly patients, although the frequency and severity of toxic effects associated with the latter are generally high [14].

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In this context, we previously conducted an elderly-specific phase II study of weekly paclitaxel combined with carboplatin, which demonstrated a reasonable response rate (45%) and less severe toxic effects (e.g. a grade 3 peripheral neuropathy rate of 3%) [15]. Next, we planned the current randomized phase II trial that involved weekly paclitaxel combined with carboplatin and compared it with standard triweekly regimen of paclitaxel combined with carboplatin for elderly patients with advanced NSCLC; this was done in order to select a proper regimen for future phase III studies that compare the efficacy of platinum doublet chemotherapy with that of single-agent chemotherapy.

patients and methods

selection of patients

Patients (age ≥70 years) with cytologically or histologically confirmed stage IIIB, stage IV, or postoperative recurrent NSCLC with measurable lesions who had never received chemotherapy or radiotherapy were enrolled in this study. Further, patients were also required to satisfy the following criteria: Eastern Cooperative Oncology Group (ECOG) performance status (PS) of zero to one, an estimated life expectancy exceeding 12 weeks, white blood cell (WBC) count of >4000/mm^3 (or a neutrophil count of >2000/mm^3), hemoglobin levels of >9.0 g/dl, platelet count of >100 000/mm^3, serum total bilirubin level of <1.5 mg/dl, serum levels of aspartate aminotransferase and alanine aminotransferase <2.0× the institutional upper limit of the normal range, serum creatinine levels of <1.5 mg/dl, and pO_2 level of >60 mmHg. We excluded patients with symptomatic brain metastasis or severe comorbidities such as symptomatic cardiovascular disease, liver cirrhosis, radiographically obvious pulmonary fibrosis, acute peptic ulcer, uncontrolled diabetes, and peripheral neuropathy. The institutional review boards of all the nine hospitals approved this study, and a written informed consent was obtained from all the enrolled patients.

treatment schedule

The enrolled patients were stratified by clinical stage (IIIB, IV, or postoperative recurrence) or ECOG PS (0 or 1) at baseline and then randomly assigned to receive the weekly paclitaxel with carboplatin arm (W arm), in which 70 mg/m^2 paclitaxel was administered once a week on days 1, 8, and 15 with carboplatin [area under the curve (AUC) = 6] on day 1 of each week, or the standard paclitaxel with carboplatin arm (S arm), in which 200 mg/m^2 of paclitaxel was administered with carboplatin (AUC = 6). Before the administration of paclitaxel, the patients were premedicated with dexamethasone (8 mg i.v.), ranitidine (50 mg i.v.), and diphenhydramine (50 mg orally) to prevent anaphylactic reaction. Carboplatin was administered immediately after paclitaxel. No prophylactic granulocyte colony-stimulating factor or prophylactic antibiotic support was planned. Paclitaxel was administered to the patients of the W arm on days 8 and 15 when the neutrophil and platelet counts exceeded 1000/mm^3 and 75 000/mm^3, respectively. The following dose reductions in the subsequent cycles were permitted in cases with the following toxic effects according to protocol: the paclitaxel dosage was reduced to 60 mg/m^2 in the W arm or 180 mg/m^2 in the S arm in case of febrile neutropenia, grade 4 neutropenia lasting 4 days, grade 2 or worse peripheral neuropathy, myalgia, or arthralgia, or grade 3 or worse non-hematological toxic effects other than nausea, vomiting, and appetite loss. Further, carboplatin was reduced to AUC 5.0 in both the arms when the platelet count decreased to <20 000/mm^3, serum creatinine levels exceeded 1.5× the institutional upper limit of the normal level, or grade 3 or worse non-hematological toxic effects were observed. To initiate subsequent cycles, the prerequisite conditions were as follows: a WBC count of >3000/mm^3 (or a neutrophil count of >1500/mm^3), platelet count of >100 000/mm^3, or non-hematological toxic effects below grade 2. A delay of the protocol treatment due to toxicity was permitted until 3 weeks. All the patients were required to receive the protocol treatment for at least three cycles unless the disease progressed, unacceptable toxicity occurred, the patients refused further treatment, or the physician decided to discontinue the treatment. Second-line chemotherapy or other treatments after this study were not prohibited by the protocol.

treatment assessment

Baseline assessment included a physical examination, complete blood counts (CBC) with differential and platelet count, hepatic and renal function tests, urine analysis, 12-lead electrocardiogram, and chest radiography. Tumor evaluation was carried out at the baseline by either a computed tomography (CT) scan or magnetic resonance imaging. During the study, the medical history and results of physical examination, weight, vital signs, ECOG PS, CBC, blood chemistry, and chest radiography were monitored on a weekly basis. Radiographic evaluation by CT scan was carried out at least every two cycles to assess the patient's response to the treatment. Unidirectional measurements were undertaken according to the RECIST criteria. The definitions of complete response (CR), partial response (PR), progressive disease (PD) and stable disease (SD) are as follows: CR, disappearance of all target lesions; PR, at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters; PD, at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study or the appearance of one or more new lesions; SD, neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. The confirmation of CR and PR required response duration of ≥4 weeks, while the confirmation of stable disease required response duration of ≥6 weeks after the initiation of the treatment. Toxic effects were assessed according to the National Cancer Institute—Common Toxicity Criteria version 2.0.

statistical analysis

The primary end point of this study was the overall response rate (ORR), and the secondary end points were the progression-free survival (PFS), overall survival, and toxicity profile. The sample size was calculated independently for each arm as follows. Assuming that an ORR of 40% in eligible patients would indicate potential usefulness, while an ORR of 20% would constitute the lower limit of interest, with $\alpha = 0.05$ and $\beta = 0.2$, the estimated accrual was 36 in each arm. Fisher's exact test was used to estimate the correlation among the different variables of the two arms. The estimation of survival was carried out using the Kaplan–Meier method and the log-rank test.

results

patient characteristics

From November 2004 to June 2007, 82 patients were enrolled from nine institutions in this study (Table 1). The median age of the patients at the time of enrollment was 75 years (range 70–87 years); 57% of the patients were ≥75 years and 15% of the patients were ≥80 years. Of the 82 patients, 69 (84%) were male and 40 (49%) had PS of one. Adenocarcinoma and squamous cell carcinoma were the most common histological types and were observed in 47% and 41% of the patients, respectively. There were 26 (31%) patients with stage IIIB, 47 (57%) with stage IV, and 9 (11%) with postoperative recurrence. There was no statistical difference in the patient characteristics of the two arms. The median number of cycles of the treatment was three cycles (range 1–6) in each arm, and

75% of the patients underwent three or more cycles in each arm. In the weekly arm, 42 patients received 139 cycles in total. Among 417 planned administrations of paclitaxel, 31 were skipped mainly because of temporary toxicity and 93% of planned doses were actually administered.

response and survival

The ORR (CR + PR) observed for the W and S arms were 55% [95% confidence interval (CI) 40% to 70%] and 53% (95% CI 38% to 68%), respectively (Table 2). There was no statistical difference in the response of the patients in the two arms. One patient in the W arm could not be evaluated for the response because the patient died due to treatment-related effects before the first evaluation of the efficacy. The median PFS and median survival time (MST) were 6.0 and 14.7 months for the patients of the W arm and 5.6 and 15.5 months for the patients of the S arm, respectively (Figure 1).

Table 1. Patient characteristics according to the treatment group

Characteristics	Weekly ($N = 42$)	Standard ($N = 40$)	Total ($N = 82$)
Age, years			
Median	74	75	75
Range	70–83	70–87	70–87
Sex			
Male	38	31	69
Female	4	9	13
ECOG PS			
0	21	21	42
1	21	19	40
Stage			
IIIB	13	13	26
IV	25	22	47
Postoperative recurrence	4	5	9
Type of histology			
Adenocarcinoma	22	17	39
Squamous cell carcinoma	15	19	34
Large cell carcinoma	4	2	6
Others	1	2	3
Number of treatment cycles			
Median	3	3	3
Range	1–6	1–6	1–6

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Response and survival according to the treatment group

	Weekly ($N = 42$), n (%)	Standard ($N = 40$), n (%)
Response		
Complete response	1 (2)	0 (0)
Partial response	22 (53)	21 (53)
Stable disease	15 (36)	14 (35)
Progressive disease	3 (7)	5 (12)
Not evaluable	1 (2)	
Overall response rate (%) (95% CI)	55 (40–70)	53 (38–68)
Disease control rate (%) (95% CI)	90 (81–99)	88 (78–98)

CI, confidence interval.

toxicity

The treatment-related grade 2 or worse toxic effects observed in this study are summarized in Table 3. Neutropenia was the most common hematological toxicity in both arms, and grade 3 or 4 neutropenia was observed in 41% and 88% of the patients in the W and S arms, respectively ($P < 0.0001$). Febrile neutropenia was observed in 2% and 10% of the patients in the W and S arms, respectively. Grade 3 peripheral neuropathy was observed in 0% and 25% of the patients in the W and S arms, respectively ($P = 0.018$). Myalgia and arthralgia also tended to be severe in the patients of the S arm. Although other non-hematological toxic effects observed were almost moderate and manageable, there was one treatment-related death in the W arm owing to drug-induced interstitial lung disease.

discussion

Although the number of elderly patients with advanced NSCLC has been increasing, the standard of care for such patients remains controversial. Randomized phase III studies of single-agent chemotherapy with drugs such as vinorelbine or gemcitabine demonstrated that the survival benefit for elderly NSCLC patients treated with this modality was higher than that

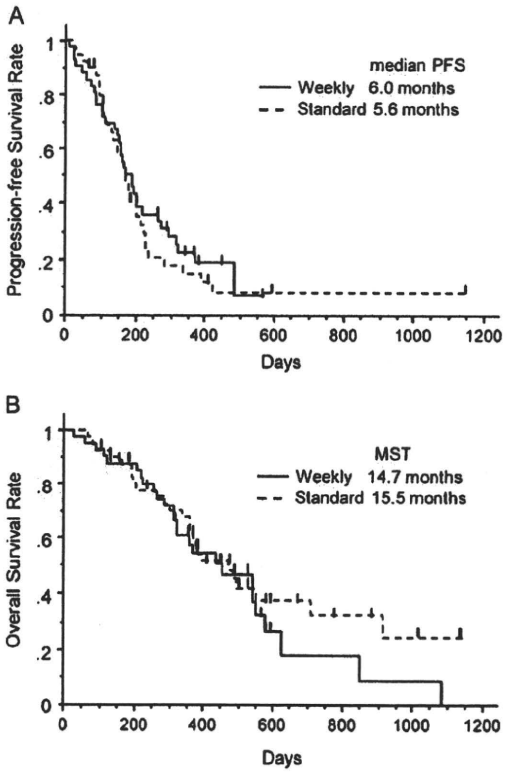

Figure 1. Progression-free survival (PFS) (A) and overall survival (B) rate in each arm.

Table 3. Adverse events (≥grade 2) according to the treatment group

Toxicity	Weekly ($N = 42$)				Standard ($N = 40$)			
	Grade 2	Grade 3	Grade 4	≥Grade 3 (%)	Grade 2	Grade 3	Grade 4	≥Grade 3 (%)
Hematological								
Neutropenia	13	14	3	41	0	11	24	88 *
Thrombocytopenia	4	2	1	7	4	2	1	8
Anemia	13	11	1	29	16	8	0	20
Non-hematological								
Febrile neutropenia	–	1	0	2	–	4	0	10 **
Peripheral neuropathy	5	0	0	0	7	10	0	25
Arthralgia, myalgia	1	0	0	0	4	3	0	8
Hyponatremia	–	2	0	5	–	5	0	13
Fatigue	0	1	0	2	4	0	0	0
Nausea/vomiting	4	2	0	5	11	5	0	13
Diarrhea	0	1	0	2	2	0	0	0
Constipation	0	1	0	2	0	0	0	0
Rash	2	0	0	0	2	0	0	0
Infection	6	2	0	2	3	2	0	5
Pneumonitis	0	0	1[a]	2	0	1	0	3
Dizziness	0	0	0	0	1	1	0	3
Cerebral infarction	0	0	0	0	0	0	1	3

[a]Treatment-related death.

*$P < 0.0001$.

**$P = 0.018$.

of the best supportive treatment [11, 12]. In addition, a recent Japanese study has indicated that docetaxel monotherapy is also suitable for elderly NSCLC patients, although the extremely high efficacy (an MST of 14.3 months) should be reexamined by another confirmatory study [13]. On the other hand, there has been no randomized study of platinum doublet chemotherapy specifically targeting the elderly population. Some retrospective analyses conducted on the subgroup of the elderly from several trials without an upper age limit have documented the benefits of platinum-based combination chemotherapy in those patients with good PS [14]. However, the percentage of the elderly population enrolled in those trials was only 30%–40%, which is much lesser than that of general practice, indicating that a selection bias clearly exists in the enrollment of elderly patients into such clinical trials in which there is no upper limit for the age of the patients. Moreover, even in those selected elderly patients with good PS, toxic effects tend to be more severe than those in younger patients, thus clearly indicating the need for elderly-specific clinical trials [16].

In this study, the patients of both the W and the S arms met the primary end point, indicating that the combination treatment of paclitaxel and carboplatin with each schedule is effective for elderly NSCLC patients. The survival data (PFS and MST) were also similar between the two arms, both of which are comparable to the results of previous trials of platinum doublet chemotherapy conducted in younger patients [3–7]. The tendency of efficacy and safety results of our study was similar to those of the phase III by Belani which also compared carboplatin plus weekly paclitaxel with carboplatin plus standard paclitaxel although most patients were <70 years old and the dose of weekly paclitaxel (100 mg/m^2/week) and the additional maintenance therapy of paclitaxel were different from our study. More than half of the patients included in our study were >75 years old which is similar to the population of elderly patients in general practice. Thus, we believe, at least for patients with good PS, the platinum doublet regimen is a reasonable choice even if they are >75 years old. Regarding the toxic effects, the incidence of grade 3/4 neutropenia and febrile neutropenia in the patients of the W arm was apparently lower than that in the patients of the S arm. The peripheral neuropathy observed in the patients of the W arm was also significantly mild and manageable as compared with that in the patients of the S arm. The results of the efficacy and safety of the present regimen comprising weekly paclitaxel were comparable to those observed in our previous study and other studies [8–10, 15, 17]. Its safety profile, in particular, is the greatest strength that may benefit elderly patients with less tolerance to chemotherapy.

Recently, Ramalingam et al. [18] reported the results of subset analysis from Belani's study specifically targeted for elderly population. Very similar to our study, they also concluded that regimen with weekly paclitaxel was equally effective and less toxic than that with standard paclitaxel in the elderly population, although the response rate of weekly regimen was less than that in our study (26% versus 55%). There are also some differences in toxic effects between the weekly regimens of each study. For example, incidences of grade 3 neuropathy, grade 3 or worse neutropenia, and anemia were 5.5%, 17%, and 16%, respectively, in Ramalingam study; meanwhile, those incidences in our study were 0%, 41%, and 29%, respectively. As to the neuropathy, dosage of paclitaxel and the maintenance therapy might have influenced the result. On the other hand, the difference of hematological toxic effects

might depend on some genetic difference between USA and Japanese patients because recent large common-arm analysis between United States and Japan revealed that Japanese patients suffered from significantly higher hematological toxic effects than USA patients even if treated with similar dose of paclitaxel and carboplatin [19].

The present study has a few limitations. The first limitation is that since the sample size used in this study was small, a definitive conclusion cannot be reached solely on the basis of the findings of this study. However, previous reports support the results obtained for each treatment conducted in this study. Since it is still unclear as to which of the two strategies of platinum doublet chemotherapy and single-agent chemotherapy is superior to the other, a larger comparative study should be conducted in future. We believe that the weekly paclitaxel and carboplatin combination used in this study may be a successful candidate as a proper platinum doublet regimen. The second limitation of this study is that we did not conduct a comprehensive geriatric assessment (CGA) or assess the quality of life of the patients in this study. The difficulty in the treatment of elderly patients is due to the heterogeneity of their comorbidities and organ functions. CGA has been recognized as a very important tool for the evaluation of the general conditions of the elderly patients; this tool must be applied in future trials for the identification and selection of a heterogeneous elderly population [20, 21]. And finally, the superiority between platinum doublet and single-agent chemotherapy in elderly population remains unclear; thus, we are now conducting the next randomized study comparing the current weekly paclitaxel with carboplatin to docetaxel alone.

In conclusion, this is the first randomized study that analyzed the efficacy and safety of the platinum doublet chemotherapy specifically designed for the elderly. In this study, the efficacy of both the treatment regimens consisting of paclitaxel and carboplatin was similar. Regarding the safety, the regimen comprising weekly paclitaxel was less toxic than that with the standard paclitaxel dosage and seems to be preferable for elderly patients with advanced NSCLC and is worthy of further investigation.

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特集 変わりゆく大腸がん化学療法—FOLFOX, FOLFIRI, そして次の10年

8. 新しいレジメンの開発状況と臨床試験

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View Points !

▶*KRAS* 野生型を対象に抗 EGFR 抗体併用に関する臨床第Ⅲ相試験が行われており，バイオマーカーによる個別化治療の方向に検討がすすんでいる。

▶ベバシズマブ併用一次治療悪化後のベバシズマブの継続投与の可否について，確認のための前向き試験が行われている。

▶術後補助化学療法に関して，内服薬や分子標的治療薬の導入に関する臨床試験が進んでいる。

▶分子標的治療薬の併用と小分子化合物の導入に関する臨床試験も行われている。

KRAS 遺伝子とセツキシマブ

- セツキシマブ（cetuximab：アービタックス®）は，上皮成長因子受容体（epidermal growth factor receptor：EGFR）に対するIgG 1型ヒト・マウスキメラ抗体で，EGFRへのリガンドの結合を阻止することで，その下流のシグナル伝達を介して起こる細胞増殖・遊走・アポトーシスの回避・血管新生などを阻害し腫瘍の進展を抑制する。
- EGFR発現陽性結腸・直腸がんを対象にした，一次治療として塩酸イリノテカン（CPT-11）／5-フルオロウラシル（5-FU）／ホリナートカルシウム（LV）併用療法（FOLFIRI療法）にセツキシマブ併用の意義を検証したCRYSTAL試験において，*KRAS* 遺伝子異常の有無によるサブセット解析がなされ，*KRAS* 野生型ではセツキシマブによる生存期間への上乗せ効果が認められるものの，*KRAS* 変異型では上乗せ効果が認めらないという結果が報告された[1]。
- 一次治療としてオキサリプラチン（L-OHP）／5-FU / LV併用療法（FOLFOX療法）にセツキシマブの併用を検討したOPUS試験[2]，化学療法不応例にbest supporting care（BSC）とセツキシマブの比較を行ったCO.17試験[3]，CPT-11抵抗性大腸がんでCPT-11とセツキシマブ標準量を投与し皮膚症状が出た症例に対して，CPT-11とセツキシマブ倍量投与の可否を検証したEVEREAT試験[4]，いずれの試験においても*KRAS* 野生型でセツキシマブによる上乗せ効果が証明された。
- いずれも後方視的解析の結果だったが，複数の解析結果が再現性を持ってセツキシマブが*KRAS* 野生型において上乗せ効果を示すことを支持したことから，NCCNのガイドラインでは*KRAS* 野生型においてセツキシマブをFOLFOXやFOLFIRI等の1次治療に使用される化学療法剤に併用す

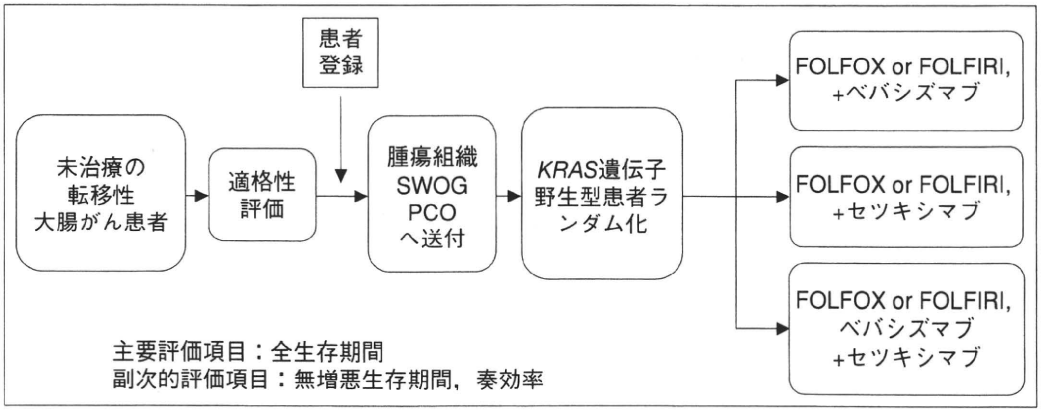

図1　CALGB／SWOG 80405試験の概要[7]

ることが推奨されている[5]。

- わが国では，セツキシマブの導入時 *KRAS* 遺伝子検索が保険適用とならなかったこともあり，大腸癌治療ガイドラインでは一次治療にセツキシマブの併用は推奨されておらず，二次治療以降の使用が推奨されている[6]。
- 現在 CALGB/SWOG 80405試験が行われている（**図1**）[7]。本試験は，*KRAS* 野生型の症例に対して標準的化学療法にベバシズマブ（beavcizumab：アバスチン®）併用群をコントロールとしてセツキシマブ併用群・ベバシズマブ／セツキシマブ同時併用群を試験アームとする比較試験である。
- 本試験の結果セツキシマブ併用群の優位が示されれば，*KRAS* 野生型の症例に対してセツキシマブ併用化学療法を第1選択として積極的に行う強いエビデンスを与えることになり，本邦の大腸がん第一次治療に関する議論が深まると考えられる。

Bevacizumab beyond progression disease（BBP）について

- 未治療転移性大腸がん患者に対してベバシズマブと化学療法併用の安全性と有効性を評価した大規模な観察的コホート研究である BRiTE（Bevazizumab Regimens : Investigation of Treatment Effects and Safety）試験において，ベバシズマブを含む一次治療で Progression disease（PD）となった後もベバシズマブを含む治療を行った群が，ベバシズマブを含まない治療ないしは無治療だった群に対して有意に生存期間が長かったことから，初回 PD 後もベバシズマブを継続すること（BBP）が生存期間の延長に繋がる可能性が示唆された[8]。
- ベバシズマブの作用メカニズムに，腫瘍血管を退縮させることで間質圧を下げ，薬剤の腫瘍到達性を改善する可能性が示唆されており，BBP の理論的根拠は存在する[9]。
- しかし，BRiTE 試験は観察試験であり，各群の割り付けにバイアスがかかっており，単に BBP 群で全身状態の良好な症例が多かっただけである可能性も否定できない。
- 標準的一次化学療法にベバシズマブを併用して PD となった症例に対して，標準的二次化学療法を行う際ベバシズマブを継続することが生存期間の延長に寄与するか否かを評価する ML18147／AIO0504試験（**図2A**）[7]と，L-OHP ベースの化学療法にベバシズマブ併用後 PD となった *KRAS* 野生型の症例に，CPT-11ベースの化学療法にベバシズマブとセツキシマブのいずれを併用した方が無増悪生存期間（progression free survival : PFS）の延長に寄与するか比較す

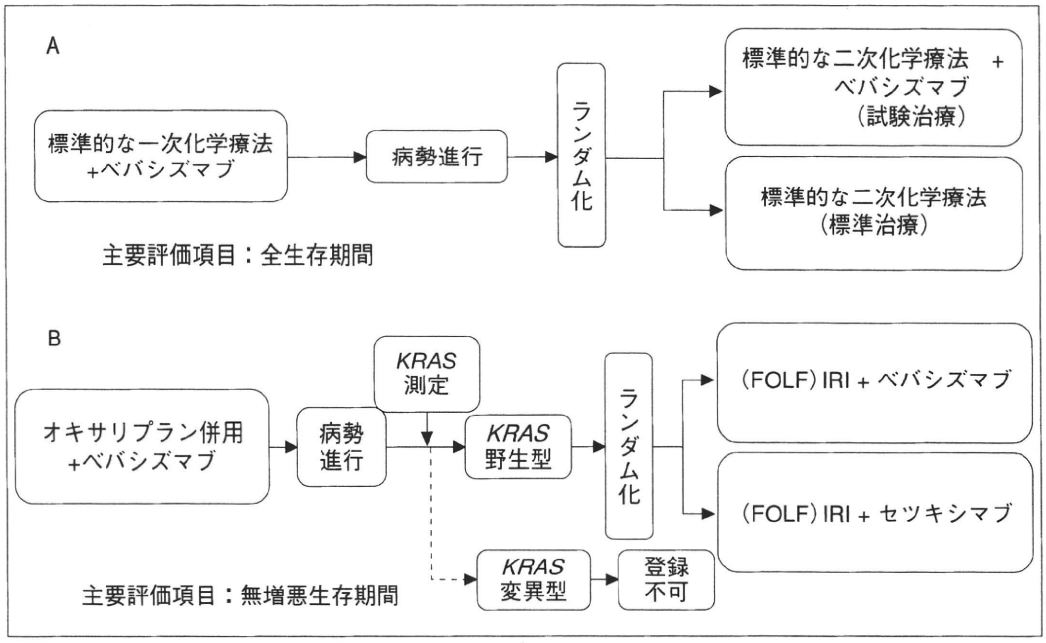

図2 BBPに関する進行中の臨床第Ⅲ相試験[7]
A：ML18147／AIO0504試験，B：SWOG S0600／iBET試験。

るSWOG S0600／iBET試験（**図2B**）[7]が現在進行中である。

- ML18147／AIO0504試験で試験治療が有意に良好となれば，BBPが日常臨床でも行われるということになると考える。また，SWOG S0600／iBET試験でもベバシズマブ群が良好となれば*KRAS*野生型でもBBPをまず考慮ということになり，いずれの試験の結果も本邦の日常臨床に影響を与えると思われる。

術後補助化学療法

- Stage Ⅱ／Ⅲ結腸がんを対象に，FOLFOX 4療法とLV5FU2療法を比較したMOSAIC試験[10]，bolus 5-FUとL-OHPの併用レジメンであるFLOX療法と5-FU/LV療法を比較したNSABP C-07試験[11]，いずれにおいてもL-OHL併用レジメンが有意に無病生存期間（disease free survival：DFS）を改善させるという結果だった。L-OHPと経口薬であるカペシタビンの併用療法であるXELOX療法とbolus 5-FU/LV療法の有用性を比較するNO16968／XELOXA試験[7]が進行中でXELOX療法が有用と判断されれば，本結果はわが国に外挿されると考えられる。
- Stage Ⅱ／Ⅲ結腸がんを対象に，mFOLFOX 6療法へのベバシズマブの上乗せ効果を検討したKSABP C-08試験では，上乗せ効果は証明されなかった[12]。しかし，現在FOLFOX 4療法とFOLFOX 4＋ベバシズマブ療法・XELOX＋ベバシズマブ療法を比較するBO17920／AVANT試験[7]にわが国も参加して世界規模で行われており，本結果はわが国の術後補助化学療法へのベバシズマブ導入に影響を及ぼすと考えられる。
- Stage Ⅲ結腸がんで*KRAS*野生型の症例を対象に，FOLFOX 4療法に対するセツキシマブの上乗せ効果を検証するPETACC-8試験[13]が欧州中心に行われている。ただし，本試験で得られる結果はセツキシマブの術後補助化学療法における位置付けを考える参考にはなるものの，手術成績の異なる欧州の結果を本邦にそのまま外挿するこ

とは，難しいと考えられる。

その他

- 標準的化学療法とベバシズマブ併用にパニツムマブ（panitumumab）の上乗せ効果をみたPACCE試験[14]でも，XELOXとベバシズマブにセツキシマブの上乗せ効果をみたCAIRO 2試験[15]でも，抗VEGF抗体と抗EGFR抗体の併用は否定的な結果だった。
- *KRAS*野生型を対象としたCALGB/SWOG 80405試験（**図1**）[7]で，本来抗EGFR抗体が有効な症例での抗VEGF抗体と抗EGFR抗体の併用効果が明らかになると考えられる。
- エルロチニブ（erlotinib：タルセバ®）などの小分子化合物を組み込んだ複数の臨床第Ⅲ相試験も展開中だが[7]，その結果によっては本邦においても小分子化合物の大腸がん治療への導入も検討されることになると考えられる。

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治療に伴う有害反応対策

Bevacizumabによる血栓症とその対策(血栓発症予測因子を含めて)

Thromboembolic events associated bevacizumab treatment

加藤俊介

Key words：bevacizumab，動脈血栓，静脈血栓，危険因子

はじめに

再発進行大腸癌の治療成績は，分子標的薬剤の登場により飛躍的に向上している．大腸癌で使用される分子標的薬剤の一つbevacizumabは，血管内皮細胞増殖因子(vascular endothelial growth factor: VEGF)に対する中和抗体であり，殺細胞効果を有する既存の抗がん剤との併用療法による長い病勢コントロール期間が可能となった．しかしその一方で既存の抗がん剤にはみられない分子標的薬剤の特有な有害事象があるため，その投与にあたっては危険因子についての十分な理解と注意が必要である．

本稿ではbevacizumabに特有な有害事象の中でも，いったん発生すると重篤化しやすい血栓症の発生メカニズムとその発症リスクについて概説する．

1. Bevacizumabによる血栓発生メカニズムについて

VEGFは生体内の血管網の構築および維持において重要な働きを担っている．血管内皮細胞における選択的なVEGFの欠失マウスを用いた解析により，VEGFのオートクライン作用が血管内皮細胞の維持に必要であることが明らかにされた[1]．この報告では，VEGFを欠失した血管内皮細胞ではアポトーシスが引き起こされていることが観察され，そのため血管内皮細胞間結合が破綻して異物面が露出するために血栓が生じると考えられている．また，VEGFシグナルを抑えることは，血小板凝集阻害因子であるprostaglandin I-2(PGI-2)や一酸化窒素(NO)の産生低下を引き起こすため，血栓形成の誘因となるとも考えられている[2]．なおVEGFシグナル阻害に関与すると考えられているbevacizumab以外の分子標的薬剤(サリドマイド＋併用化学療法など)においても血栓症のリスクは増大することが報告されており，これら薬剤においても同様の血栓発生メカニズムが働くものと示唆される[3]．

2. 動脈血栓塞栓症

bevacizumab投与により動脈血栓塞栓症の発生頻度が増加することは，これまで複数の癌種の臨床試験を統合解析した結果から報告されている．2007年Scappaticciらは**表1**に挙げた大腸癌，乳癌，非小細胞肺癌1,745例からなる5つのランダム化比較試験を対象として動脈血栓塞栓症についての発症リスク解析を行った[4]．963例はbevacizumab投与群に，782例は対照

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表1 動脈血栓塞栓症：試験別発症リスク（文献[4]より改変）

試験	癌種	化学療法レジメン	対照群		bevacizumab投与群		ハザード比
			イベント発生数	治療例数	イベント発生数	治療例数	
AVF2107g	大腸癌	IFL, FU/LV*	5	396	20	501	
AVF2119g	乳癌	capecitabine	1	215	1	229	
AVF2192g	大腸癌	FU/LV	5	104	10	100	
AVF0780g	大腸癌	FU/LV	1	35	3	67	
AVF0757g	非小細胞肺癌	CBDCA/PTX	1	32	3	66	
総計			13	782	37	963	2.0(95%CI: 1.05-3.75)

*FU/LV療法はbevacizumab群のみ.

表2 動脈血栓塞栓症危険因子（文献[4]より改変）

危険因子	比較	単変量HR(95%CI)	p値	多変量HR(95%CI)	p値
bevacizumabの投与	あり/なし(782/963)	1.99(1.05-3.75)	0.03	1.95(1.04-3.67)	0.04
年齢	65歳以上/65歳未満(618/1,127)	3.00(1.69-5.30)	<0.001	2.17(1.17-4.01)	0.01
性別	男性/女性(760/985)	0.57(0.32-1.01)	0.05		
ベースラインにおける高血圧	あり/なし(799/946)	1.89(1.06-3.34)	0.03		
動脈血栓塞栓症の既往	あり/なし(148/1,597)	5.18(2.86-9.39)	<0.001	3.65(1.92-6.92)	<0.001
粥状硬化症の既往	あり/なし(192/1,553)	4.17(2.32-7.49)	<0.001		
糖尿病の既往	あり/なし(224/1,521)	1.91(0.98-3.73)	0.06		
心筋梗塞の既往	あり/なし(110/1,635)	4.90(2.56-9.38)	<0.001		
脳卒中または一過性脳虚血発作の既往	あり/なし(25/1,720)	3.16(0.77-13.0)	0.11		
静脈血栓の既往	あり/なし(79/1,666)	0.47(0.07-3.41)	0.46		

群に無作為化割り付けされており，動脈血栓塞栓イベントの発生割合は対照群で1.7％に対してbevacizumab投与群では3.8％と約2倍高いことが報告された(ハザード比2.0，95%CI 1.05-3.75，p=0.031)．更に危険因子について多変量解析を行った結果，血栓症の発症リスクとしてbevacizumabの投与，動脈血栓塞栓症の既往，65歳以上が独立した因子として挙げられた(**表2**)．なおこの解析では，動脈血栓塞栓症の既往，65歳以上のリスクを保有していても無増悪生存期間，生存期間に対するbevacizumabの効果は全症例と同等であったことも報告されている．

更に2010年Ranpuraらは対象患者を増やして動脈血栓発症リスクについて詳細な報告を行っている[5]．それによると対照群で2.0％(95% CI 1.7-2.5％)，bevacizumab投与群では3.3％(95%CI 2.0-5.6％)，ハザード比は1.44(95% CI 1.08-1.91，p=0.013)とScappaticciらと同様，bevacizumab投与により動脈血栓発症リスクは高まることを報告している．なおこの研究ではbevacizumabの投与用量ごとによる動脈血栓塞栓症のリスク評価もなされたが，2.5 mg/kg/週群と対照群でハザード比1.52(95%CI 1.10-2.09)，5mg/kg/週群と対照群ではハザード比1.50(95%CI 0.83-2.69)と，投与量の増加によるリスクの増大は観察されなかった．癌種別で発症リスクを比較すると，すべてのグレードについては大腸癌で発生率が高く，重篤なものになると非小細胞肺癌，膵癌，腎臓癌で高い傾向であった．また動脈血栓塞栓症の中で心筋虚血は対照群と比べて明らかに発生頻度が高い(RR 2.14，95%CI 1.12-4.08，p=0.021)が，

脳虚血は有意ではなかった(RR 1.37，95%CI 0.67−2.79，p=0.39)ことも報告されている．

3．静脈血栓塞栓症

動脈血栓塞栓症と異なり，静脈血栓塞栓症の発症リスクについては異なる報告が出されており一定の見解に至っていないと思われる．

前述のScappaticciらの解析[4]では，静脈血栓塞栓症の発症リスクはbevacizumab投与でも上昇しないという結果を報告している．更に，2010年Cassidyらは10件の臨床試験6,055人(bevacizumab投与群3,448人，対照群2,607人：非小細胞肺癌1,084人，腎癌641人，膵癌583人，大腸癌2,573人，乳癌1,174人)のデータを用いて解析を行い報告している[6]が，静脈血栓塞栓症の発症率はbevacizumab投与群で10.9％，化学療法単独群で9.8％とほぼ同等であった(RR 1.14，95%CI 0.96−1.35)．更に治療期間で補正して調整した後の静脈血栓塞栓症の発症についても有意な差が認められなかったことが報告されている．

しかし，Nalluriらは同じく10件の臨床試験データ(7,956人，bevacizumab投与群4,292人，対照群3,664人：非小細胞肺癌2,090人，腎癌641人，大腸癌3,437人，乳癌1,156人，中皮腫633人)によるメタ解析を行った結果，静脈血栓塞栓症の発症率はbevacizumab投与群で8.3％，化学療法単独群で6.1％と(RR 1.33，95% CI 1.13−1.56)，bevacizumab投与群で静脈血栓塞栓症の発症リスクは上昇するという，Scappaticciらとは異なる結果を報告している[7]．また，こちらの報告ではbevacizumabの投与用量ごとの違いによる静脈血栓塞栓症の発症頻度については，動脈血栓塞栓症同様に差はみられなかった．

4．血栓発症対策

前述したScappaticciらの報告[4]では，解析した試験で低用量のアスピリンの投与は許容されていたことから，アスピリンの使用と動脈血栓塞栓イベントの発生率について算出されている．アスピリン使用例の背景には動脈血栓塞栓イベントの既往が多いことを考慮して考える必要があるが，アスピリン非使用例ではbevacizumab投与により明らかに動脈血栓塞栓のイベントが増加する(1.7％ vs 3.6％，OR 2.15，95%CI 1.09−4.24，p=0.03)のに対し，アスピリン使用例ではbevacizumab投与により動脈血栓塞栓は増加する傾向はみられるものの統計学的な有意差がみられなかった(1.2％ vs 5.1％，OR 4.50，95%CI 0.54−37.27，p=0.16)ことが報告されており，一定の効果はみられる可能性はある．しかし，全体のイベント発生数やアスピリン使用症例が少なかったため，予防効果についての明確な結論は出せなかった．なお，同報告においてはアスピリン使用による出血リスクの増大はみられなかったとされている．

おわりに

bevacizumabによる動静脈血栓塞栓症発症リスクについて大規模試験の統合解析をもとに概説してきた．静脈血栓塞栓症についてはその発症リスクがbevacizumab投与により上昇するか意見は分かれているが，動脈血栓塞栓症発症リスクはいずれの報告においてもリスクが高まることが報告されている．動脈血栓塞栓症の中でも特に心筋虚血は，いずれの解析においてもbevacizumab投与により有意に高くなるため，高リスク群とされている65歳以上，血栓症の既往がある患者に対しては要注意である．しかし，これらリスクをもっている患者においても，bevacizumab投与による生存期間の延長がみられたことから，十分なリスクとベネフィットに対する評価を行ったうえでbevacizumab使用の是非を検討する必要があるものと思われる．

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ORIGINAL ARTICLE

Phase II study of FOLFOX4 with "wait and go" strategy as first-line treatment for metastatic colorectal cancer

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Abstract
Purpose To evaluate the efficacy and safety of FOLFOX4 using "wait and go" strategy in treating metastatic colorectal cancer.
Methods The conventional FOLFOX4 was repeated every 2 weeks. We waited until the recovery of symptoms from persistent neurotoxicity within an added period of 2 weeks, before performing the next cycle ("wait and go" strategy).
Results We enrolled 58 patients, in whom a total of 481 cycles were administered (median 8 per patient; range 1–16). Toxicity was evaluated in 58 patients and response in 55. The major toxic effect was grade 3/4 neutropenia (33%). Painful paresthesia or persistent functional impairment was observed in 4 patients (7%). The response rate was 40% (95% confidence interval; 27.1–52.9%). The median progression-free survival time was 10.2 months, the 1-year survival rate was 89%, and the median overall survival time was 27.6 months.
Conclusions These findings indicate that this "wait and go" strategy reduces the frequency of persistent neuropathy while maintaining efficacy against metastatic colorectal cancer.

Keywords FOLFOX · Neuropathy · Metastatic colorectal cancer · Oxaliplatin · "Wait and go"

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