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Clinical Trial Results

Randomized Phase II Study of Weekly Paclitaxel plus Carboplatin Versus Biweekly Paclitaxel plus Carboplatin for Patients with Previously Untreated Advanced Non-Small Cell Lung Cancer

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Trial Information

- **ClinicalTrials.gov Identifier**: UMIN000036556
- **Sponsor(s)**: Clinical Research Support Center Kyushu
- **Principal Investigator**: Koichi Takayama
- **IRB Approved**: Yes

Lessons Learned

- This clinical trial, evaluating the efficacy and safety of a carboplatin plus paclitaxel regimen in a biweekly or weekly schedule instead of the more toxic 3-weekly administration, showed that the weekly regimen was better in efficacy than the biweekly regimen, with mild toxicities, for patients with non-small cell lung cancer (NSCLC).
- The weekly carboplatin plus paclitaxel regimen could be considered as an alternative to the 3-weekly regimen in Japanese patients with NSCLC.

Abstract

Background. Combination therapy comprising carboplatin (C) and paclitaxel (P) is the most commonly used regimen for the treatment of advanced non-small cell lung cancer (NSCLC). Common toxicities associated with the regimen, such as neuropathy and myelosuppression, cause its discontinuation. In the present study, we conducted a clinical trial evaluating the efficacy of biweekly (B) and weekly (W) PC therapy to identify the appropriate chemotherapy schedule for Asian patients.

Methods. Chemonaive patients with IIIB/IV NSCLC and a performance status of 0–1 were randomly assigned to a biweekly regimen (paclitaxel 135 mg/m^2 with carboplatin area under the curve [AUC] 3 on days 1 and 15 of every 4 weeks) or to a weekly regimen (paclitaxel 90 mg/m^2 on days 1, 8, and 15 with carboplatin AUC 6 on day 1 of every 4 weeks).

Results. A total of 140 patients were enrolled in the study. The objective response rates (ORRs) were 28.1% (B) and 38.0% (W). The most common toxicity was neutropenia, with incidence rates of 62.0% (B) and 57.8% (W). Progression-free survivals (PFSs) were 4.3 months (B) and 5.1 months (W), and overall survival durations were 14.2 months (B) and 13.3 months (W).

Conclusion. The ORR and PFS in the weekly regimen were better than those in the biweekly schedule, although a statistical difference was not observed. The toxicity profile was generally mild for both regimens. The weekly CP regimen was suitable to be considered as an alternative to the current 3-weekly regimen in NSCLC treatment. ***The Oncologist*** 2019;24:1420–e1010

Discussion

Lung cancer is one of the leading causes of death in many Asian countries [1–3]. For patients with advanced NSCLC, systemic chemotherapy remains the standard care. The combination of C and P is the most commonly used regimen for the treatment of advanced NSCLC, and its efficacy has been established by randomized phase III studies [4–6]. The Eastern Cooperative Oncology Group (ECOG) study that compared four commonly used regimens for first-line therapy of advanced NSCLC demonstrated similar efficacy, including median survival and 1-year survival in all four regimens [6]. A similar clinical trial comparing four different platinum doublets including a CP regimen was performed in Japan [7]. The results of this study demonstrated a favorable tolerability profile and a similar efficacy in the CP regimen (PFS: 4.5 months; OS: 12.3 months). The most common nonhematological toxicities associated with the CP regimen were neuropathy and arthralgia. In particular, severe neuropathy caused the

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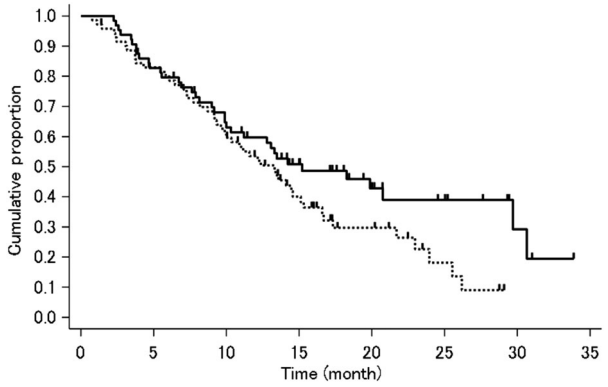

Figure 1. Overall survival (OS) curve by the Kaplan-Meier method. Solid and dotted lines indicate the biweekly and weekly arms, respectively. The median OS in the biweekly and weekly arms was 14.2 months (95% confidence interval [CI]: 9.9–25.4 months) and 13.3 months (95% CI: 9.9–15.3 months), respectively. No significant differences were noted in either arm (p = .10, log-rank test).

deterioration of daily activity and quality of life. To improve the tolerability profile of this regimen, dose reduction of paclitaxel or administration of paclitaxel on a split schedule has been recommended [8, 9]. Administration of paclitaxel on a weekly basis for 3 out of 4 weeks in combination with carboplatin on day 1 of an every-4-week cycle was associated with the most favorable therapeutic index among three regimens tested [9]. A phase III study comparing a weekly PC regimen and a 3-weekly PC regimen showed a similar efficacy with favorable nonhematologic toxicity in the weekly PC regimen [10]. More frequent grade 3 or 4 neutropenia, febrile neutropenia, and anemia were observed in the Japanese population than in the white population, despite the lower treatment delivery [11]. Because there is a clear ethnic difference in hematological toxicities, we initially conducted a single-arm phase II study of a CP regimen in which administration of carboplatin and paclitaxel was performed on a biweekly schedule. The dose of the CP regimen was determined by AUC 3 added with 140 mg/m^2 according to a phase I study reported previously [12]. The biweekly administration of the CP regimen was associated with favorable therapeutic efficacy (response rate: 35.1%; median survival: 357 days) in the previous phase II study [13]. Moreover, this study showed a reduction in neurotoxicity and myelosuppression compared with the 3-weekly regimen reported previously [7]. On the basis of these results, we conducted the present randomized phase II study to compare the efficacy and safety of the weekly and biweekly CP regimen for patients with advanced NSCLC.

This phase II study was developed with the intent of reducing toxicity while maintaining efficacy similar to that in the standard 3-weekly regimen. The ORR was 28.1% in the biweekly arm and 38.0% in the weekly arm (p = .27). Median PFS was 4.3 months in the biweekly arm and 5.1 months in the weekly arm (p = .24). Median OS was 14.2 months in the biweekly arm and 13.3 months in the weekly arm (p = .10). Both regimens had results comparable to the previously described 3-weekly regimen. There were no statistically significant differences in the primary endpoint ORRs, but the weekly regimen tended to be superior to the biweekly regimen. In the secondary endpoints, the weekly regimen tended to be favorable for PFS and hematologic toxicities, but the biweekly regimen tended to be favorable for OS (Fig. 1), both of which were not statistically significant. For treatment delivery, in the biweekly arm, the average number of cycles was 2.8 and 45% of patients received 4 cycles, and in the weekly arm, the average number of cycles was 3.0 and 53% of patients received 4 cycles. Based on these results, the weekly CP regimen could be considered as an alternative to the 3-weekly regimen in NSCLC.

Trial Information	
Disease	Advanced cancer
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	None
Type of Study – 1	Phase II
Type of Study – 2	Randomized
Primary Endpoint	Overall response rate
Secondary Endpoint	Progression-free survival
Secondary Endpoint	Overall survival
Secondary Endpoint	Toxicity
Additional Details of Endpoints or Study Design	
The primary efficacy endpoint was the ORR. The secondary efficacy endpoints were PFS, OS, and toxicities. The sample size was calculated based on the assumption of an objective response rate of 25% as the threshold and 40% in the experimental regimens to ensure the power of 80%. Patients were stratified by stage and sex at enrollment.	
Patient demographics and baseline history were summarized per treatment arm, with descriptive statistics for continuous measures and counts and frequencies for categorical variables. The ORR was defined as the percentage of patients achieving complete response (CR) or partial response (PR). The difference of the ORR was analyzed by Fisher's exact test. OS and PFS were characterized using Kaplan-Meier equations and analyzed by log-rank test. Toxicity by grade was tabulated per treatment arm.	
Investigator's Analysis	Active and should be pursued further

Drug Information for Phase II Biweekly	
Drug 1	
Generic/Working Name	Carboplatin
Drug Class	Platinum compound
Dose	AUC 3 mg per mL × minute
Route	IV
Schedule of Administration	Biweekly; paclitaxel 135 mg/m^2 with carboplatin AUC of 3 mg/mL × minute biweekly for 2 of 4 weeks of each 28-day cycle
Drug 2	
Generic/Working Name	Paclitaxel
Dose	135 mg/m^2
Route	IV
Schedule of Administration	Biweekly; paclitaxel 135 mg/m^2 with carboplatin AUC of 3 mg/mL × minute biweekly for 2 of 4 weeks of each 28-day cycle

Drug Information for Phase II Weekly	
Drug 1	
Generic/Working Name	Carboplatin
Trade Name	
Company Name	
Drug Type	
Drug Class	Platinum compound
Dose	AUC 6 mg per mL × minute
Route	IV
Schedule of Administration	Weekly, paclitaxel 90 mg/m^2 weekly for 3 of 4 weeks with carboplatin AUC of 6 mg/mL × minute on day 1 of each 28-day cycle
Drug 2	
Generic/Working Name	Paclitaxel
Trade Name	
Company Name	
Drug Type	
Drug Class	
Dose	90 mg/m^2
Route	IV
Schedule of Administration	Weekly, paclitaxel 90 mg/m^2 weekly for 3 of 4 weeks with carboplatin AUC of 6 mg/mL × minute on day 1 of each 28-day cycle

Patient Characteristics: Phase II Biweekly	
Number of Patients, Male	45
Number of Patients, Female	19
Stage	Stage (IIIB/IV); (12/52)
Age	Median (range): 64
Number of Prior Systemic Therapies	Median (range): not collected
Performance Status: ECOG	0 — 34 1 — 30 2 — 0 3 — 0 Unknown — 0

Cancer Types or Histologic Subtypes	Adenocarcinoma, 47 Squamous cell carcinoma, 14 NOS, 3

Patient Characteristics: Phase II Weekly	
Number of Patients, Male	48
Number of Patients, Female	23
Stage	Stage (IIIB/IV); (13/58)
Age	Median (range): 66
Performance Status: ECOG	0 — 32 1 — 39 2 — 0 3 — 0 Unknown — 0
Cancer Types or Histologic Subtypes	Adenocarcinoma, 49 Squamous cell carcinoma, 14 NOS, 8

Primary Assessment Method: Phase II Biweekly	
Title	ORR
Number of Patients Enrolled	64
Number of Patients Evaluable for Toxicity	64
Number of Patients Evaluated for Efficacy	64
Evaluation Method	RECIST 1.0
Response Assessment CR	*n* = 0 (0%)
Response assessment PR	*n* = 18 (28.1%)
Response Assessment SD	*n* = 27 (42.2%)
Response Assessment PD	*n* = 16 (25.0%)
Response Assessment OTHER	*n* = 3 (4.7%)
(Median) Duration Assessments PFS	4.3 months, CI: 3.5–5.3
(Median) Duration Assessments OS	14.2 months, CI: 9.9–25.4
Outcome Notes	
The ORR was 28.1% in the biweekly arm and 38.0% in the weekly arm (p = .27). Median PFS was 4.3 months in the biweekly arm and 5.1 months in the weekly arm (Fig. 2). No statistical difference in the response rate and PFS in the biweekly and weekly regimens was noted. Median OS was 14.2 months in the biweekly arm and 13.3 months in the weekly arm. OS in the biweekly arm was slightly, but not significantly, longer than that in the weekly arm.	

Primary Assessment Method: Phase II Weekly	
Title	ORR
Number of Patients Enrolled	71
Number of Patients Evaluable for Toxicity	71
Number of Patients Evaluated for Efficacy	71
Evaluation Method	RECIST 1.0
Response Assessment CR	*n* = 0 (0%)

Response Assessment PR	*n* = 27 (38.0%)
Response Assessment SD	*n* = 23 (32.4%)
Response Assessment PD	*n* = 12 (16.9%)
Response Assessment OTHER	*n* = 9 (12.7%)
(Median) Duration Assessments PFS	5.1 months, CI: 4.0–6.6
(Median) Duration Assessments OS	13.3 months, CI: 9.9–15.3

Outcome Notes

The ORR was 28.1% in the biweekly arm and 38.0% in the weekly arm (p = .27). Median PFS was 4.3 months in the biweekly arm and 5.1 months in the weekly arm. No statistical difference in the response rate and PFS in the biweekly and weekly regimens was noted. Median OS was 14.2 months in the biweekly arm and 13.3 months in the weekly arm. OS in the biweekly arm was slightly, but not significantly, longer than that in the weekly arm.

Adverse Events: Phase II Biweekly

All Cycles

Name	NC/NA	1	2	3	4	5	All grades
Leukocytes (total WBC)	29%	20%	34%	17%	0%	0%	71%
Neutrophils/granulocytes (ANC/AGC)	15%	5%	22%	33%	25%	0%	85%
Hemoglobin	13%	56%	28%	3%	0%	0%	87%
Platelets	59%	39%	2%	0%	0%	0%	41%
AST, SGOT	65%	27%	8%	0%	0%	0%	35%
ALT, SGPT	54%	34%	9%	3%	0%	0%	46%
Bilirubin (hyperbilirubinemia)	87%	11%	2%	0%	0%	0%	13%
Creatinine	91%	9%	0%	0%	0%	0%	9%
Sodium, serum-low (hyponatremia)	38%	59%	0%	3%	0%	0%	62%
Potassium, serum-high (hyperkalemia)	63%	31%	6%	0%	0%	0%	37%
Proteinuria	95%	3%	2%	0%	0%	0%	5%
Nausea	62%	22%	11%	5%	0%	0%	38%
Constipation	59%	33%	8%	0%	0%	0%	41%
Hair loss/alopecia (scalp or body)	26%	44%	30%	0%	0%	0%	74%
Neuropathy: sensory	54%	37%	6%	3%	0%	0%	46%
Infection with unknown ANC	82%	2%	2%	14%	0%	0%	18%
Diarrhea	91%	6%	0%	3%	0%	0%	9%

Neutropenia was the most common hematologic toxicity in total, with no statistical difference between the weekly and biweekly arms. In grade ≥3 toxicities, incidence rates of anemia, leucopenia, and thrombocytopenia were significantly higher in the weekly arm compared with those in the biweekly arm (28.2% vs. 3.1% [p < .01], 35.2% vs. 17.2% [p < .05], and 8.5% vs. 0% [p < .05], respectively). Nonhematological toxicities were generally mild and manageable. However, it is important to note that the frequency of infection was significantly higher in the biweekly arm (1.4% vs. 14.1% [p < .01]).

Abbreviations: AGC, absolute granulocyte count; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; NC/NA, no change from baseline/no adverse event; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; WBC, white blood cell.

Adverse Events: Phase II Weekly

All Cycles

Name	NC/NA	1	2	3	4	5	All grades
Leukocytes (total WBC)	11%	10%	44%	32%	3%	0%	89%
Neutrophils/granulocytes (ANC/AGC)	15%	8%	21%	46%	10%	0%	85%
Hemoglobin	3%	28%	41%	27%	1%	0%	97%
Platelets	36%	45%	10%	6%	3%	0%	64%
AST, SGOT	53%	41%	3%	3%	0%	0%	47%
ALT, SGPT	46%	41%	7%	6%	0%	0%	54%
Bilirubin (hyperbilirubinemia)	91%	7%	1%	1%	0%	0%	9%
Creatinine	87%	13%	0%	0%	0%	0%	13%

Sodium, serum-low (hyponatremia)	25%	62%	0%	13%	0%	0%	75%
Potassium, serum-high (hyperkalemia)	69%	28%	3%	0%	0%	0%	31%
Proteinuria	91%	6%	3%	0%	0%	0%	9%
Nausea	43%	42%	11%	4%	0%	0%	57%
Constipation	70%	24%	6%	0%	0%	0%	30%
Diarrhea	75%	17%	8%	0%	0%	0%	25%
Infection with unknown ANC	91%	1%	7%	1%	0%	0%	9%
Hair loss/alopecia (scalp or body)	32%	54%	14%	0%	0%	0%	68%
Neuropathy: sensory	64%	32%	3%	1%	0%	0%	36%

Neutropenia was the most common hematologic toxicity in total, with no statistical difference between the weekly and biweekly arms. In grade ≥3 toxicities, incidence rates of anemia, leucopenia, and thrombocytopenia were significantly higher in the weekly arm compared with those in the biweekly arm (28.2% vs. 3.1% [$p < .01$], 35.2% vs. 17.2% [$p < .05$], and 8.5% vs. 0% [$p < .05$], respectively). Nonhematological toxicities were generally mild and manageable. However, it is important to note that the frequency of infection was significantly higher in the biweekly arm (1.4% vs. 14.1% [$p < .01$]).

Abbreviations: AGC, absolute granulocyte count; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; NC/NA, no change from baseline/no adverse event; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; WBC, white blood cell.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Active and should be pursued further

The efficacy and toxicity data of the 3-weekly carboplatin plus paclitaxel (CP) regimen in the Japanese population is available in several clinical trials, including the FACS trial [7], NEJ002 trial [15], and JO19907 trial [16]. Clinical data of carboplatin plus paclitaxel in Asian populations are available from the reference arm in the IPASS study conducted in nine countries in Asia [17]. The objective response rate (ORR) data in these clinical trials were 32.4% (FACS), 29.0% (NEJ002), 31.0 (JO19907), and 32.2% (IPASS). The ORR of 37.6% in the weekly arm of this study was similar to that reported by the previous clinical trials. The present findings suggest that patients with advanced non-small cell lung cancer (NSCLC) may obtain a similar efficacy from the split dose of the CP regimen with a weekly schedule. Toxicities associated with this dose were clearly lesser. Hematologic toxicities except anemia and neurotoxicity were mild compared with those in the 3-weekly CP regimen reported previously [7]. In terms of survival, overall survival (OS) was better in the biweekly arm and correlated inversely with improved progression-free survival (PFS) in the weekly arm. The discrepancy between OS and PFS data may be due to the difference in poststudy treatment. The prevalence of second-line chemotherapy was 55% and 59% in the weekly and biweekly arms, respectively. The rate of use of epidermal growth factor receptor tyrosine kinase inhibitors or docetaxel as a second-line chemotherapy in both arms was not statistically different. Moreover, there was no difference between the actual doses of carboplatin and paclitaxel. Another explanation is that more severe toxicities reduced the survival rate in the weekly arm. As shown in the Adverse Events section, grade 3 or 4 hematological toxicities in the weekly arm were significantly more severe than those in the biweekly arm. The association of chemotherapy-induced neutropenia and treatment efficacy was reported previously [18, 19].

The addition of bevacizumab to the regimen of carboplatin and paclitaxel was confirmed to improve the survival of patients with advanced nonsquamous NSCLC [20]. However, a higher incidence of neutropenia was reported with the three-drug combination treatment, especially in older patients [20, 21]. In the Japanese population, a randomized phase II study comparing CP regimens with and without bevacizumab showed a similar toxicity profile [16]. The addition of bevacizumab increased the incidence of grade 4 neutropenia from 57% to 73%. Split doses of paclitaxel may provide a favorable toxic profile compared with the bevacizumab-based therapy. Carboplatin plus weekly paclitaxel in combination with bevacizumab was well tolerated in patients with metastatic melanoma in a phase II study [22], although comparative data were not available for patients with lung cancer in this setting. The CP regimen with split dose may thus be an alternative with a better toxicity profile for patients with NSCLC. A phase III comparative study with the 3-weekly regimen has been planned as a future course of action.

Acknowledgments

We thank the staff of the Clinical Research Support Center Kyushu for their secretarial assistance and for preparing the manuscript.

Disclosures

Koichi Takayama: Chugai-Roche Co., Ono Pharmaceutical Co. (RF), AstraZeneca, Chugai-Roche Co., MSD-Merck Co., Eli Lilly Co., Boehringer-Ingelheim Co., DaiichiSankyo Co. (H); **Junji Uchino:** AstraZeneca, Eli Lilly Japan K.K. (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Figure

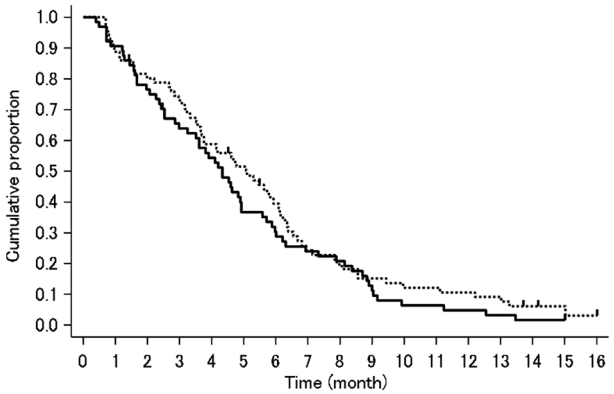

Figure 2. Progression-free survival (PFS) curve by the Kaplan-Meier method. Solid and dotted lines indicate the biweekly and weekly arms, respectively. The median PFS in the biweekly and weekly arms was 4.3 months (95% confidence interval [CI]: 3.5–5.3 months) and 5.1 months (95% CI: 4.0–6.6 months), respectively. No significant differences were noted in either arm (p = .29, log-rank test).