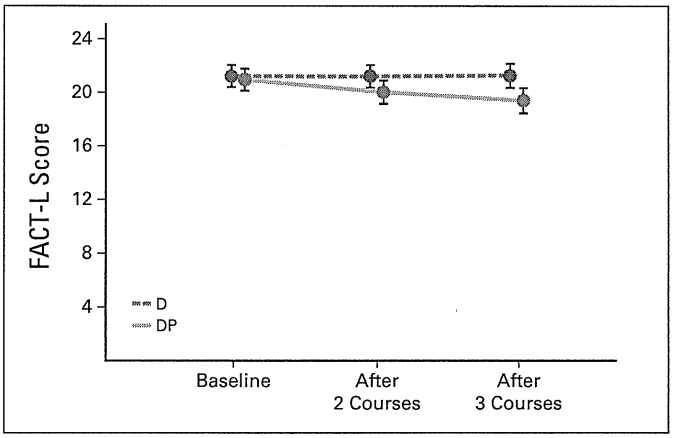

Fig 3. Quality-of-life assessments according to the seven-item Functional Assessment of Cancer Therapy–Lung (FACT-L). Dots and error bars indicate the least squared mean total scores and 95% CI, respectively. Higher scores indicate a better quality of life. D, docetaxel; DP, docetaxel plus cisplatin.

numbers of patients with missing data because of death or severe deterioration of the patient's general condition in the docetaxel and DP arms were one and six patients, respectively, after the second cycle and six and nine patients, respectively, after the third cycle. In the docetaxel and DP arms, 39.3% (53 of 135 patients) and 36.8% (50 of 136 patients) of patients had scores that improved from baseline to the end of the third cycle, which did not constitute a significant difference. Although the mean total score remained near its baseline value in the docetaxel arm, it declined gradually in the DP arm, changing in a statistically significant manner between baseline and cycle 3 ($P < .01$; Fig 3).

Supplementary Ad Hoc Analysis

Data forms were collected from 275 patients (except one patient from the docetaxel arm). *EGFR* mutation testing was performed in 79 patients (58%) and 74 patients (53%) in the docetaxel and DP arms, respectively; the results revealed active *EGFR* mutations in 22 patients in the docetaxel arm (16% overall and 28% of those tested) and 16 patients in the DP arm (12% overall and 22% of those tested). After protocol treatment completion, further drug treatment was administered to 74 patients (54%) in the docetaxel arm and 70 patients (50%) in the DP arm. During this treatment, EGFR tyrosine kinase inhibitor was administered to 35 patients (26%) and 23 patients (17%) in the docetaxel and DP arms, respectively.

Figure 4 shows the survival HRs according to subgroup analyses of the baseline and ad hoc characteristics. No significant differences between the two treatment groups were observed in any subgroup.

DISCUSSION

The standard treatment for fit patients with advanced NSCLC is platinum-doublet chemotherapy.[6,7] Several retrospective subgroup analyses have shown that platinum-doublet chemotherapy is similarly effective in elderly and younger patients and is well tolerated despite an increased incidence of toxicity.[9,10] These retrospective analyses, however, were performed in highly selected elderly populations. Generally, elderly patients are often unsuitable candidates for bolus cisplatin administration because of comorbid illnesses and/or organ dysfunction. Therefore, we considered it important to conduct a prospective investigation to determine whether the addition of a modified platinum agent might improve survival in elderly patients with NSCLC.

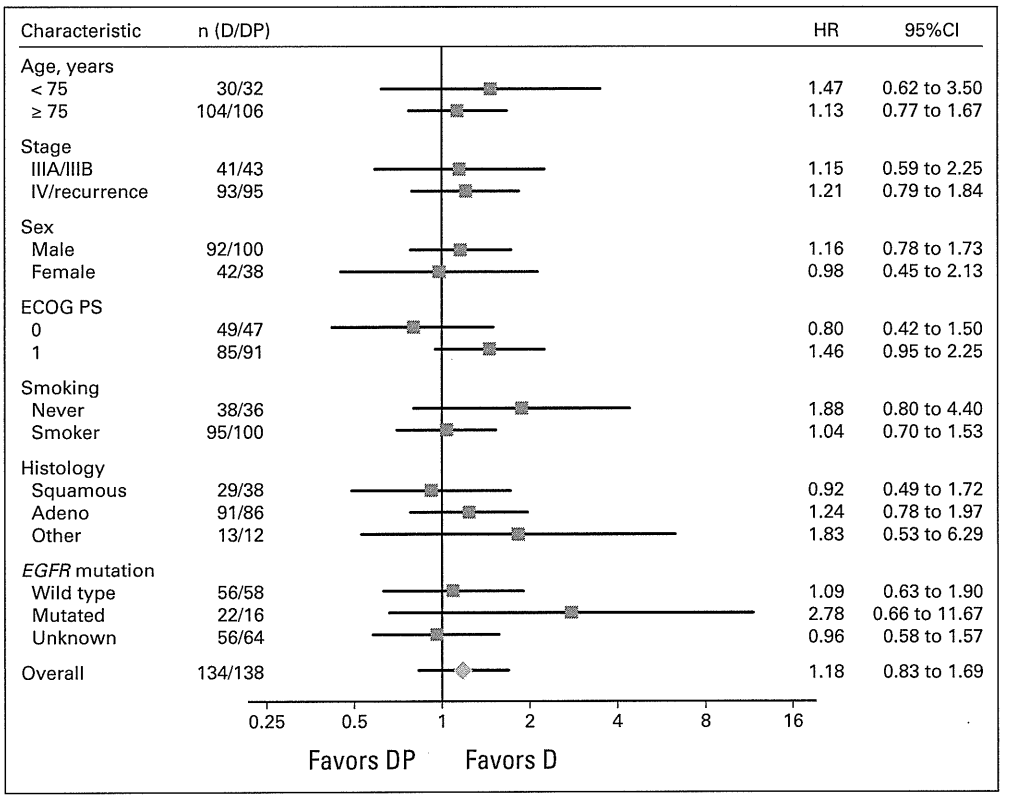

Fig 4. Subgroup analysis of overall survival. D, docetaxel; DP, docetaxel plus cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

In the phase II and previous phase III trials, we demonstrated that weekly split docetaxel and additional cisplatin reduced myelotoxicity and increased RRs.[13,14] In this study, we analyzed the add-on effect of weekly cisplatin over docetaxel monotherapy. Although the DP arm tended to have higher RRs than the docetaxel arm, this was reflected in neither the PFS nor the OS.

Although we collected information on comorbid illnesses, we did not assess the Charlson comorbidity index. Comprehensive geriatric assessments, including basic activities of daily living (ADLs), instrumental ADLs, Mini-Mental State Examination, and Geriatric Depression Scale evaluation, were also conducted for exploratory purposes. Although the prognostic values of these assessments have not been validated for elderly patients with lung cancer, it was suggested that ADLs and Mini-Mental State Examination can be useful.[18] In future research, we should evaluate these factors prospectively.

The proportions of female patients and patients with adenocarcinoma were slightly higher in the docetaxel arm than in the DP arm. In eastern Asia, including Japan, active *EGFR* mutations are often observed in such patients and have been reported as a favorable prognostic factor in patients with NSCLC.[19,20] According to a subgroup analysis, the median survival time was 12.8 months in the 114 patients (in the docetaxel plus DP arms) without *EGFR* mutation and 24.1 months in the 38 mutation-positive patients. The proportion of patients with active *EGFR* mutations was slightly higher in the docetaxel arm than in the DP arm. However, it would have been difficult to demonstrate the superiority of the DP arm in OS, considering the slight difference in PFS, even if there were no such imbalances.

In the docetaxel arm, a higher proportion of patients required dose reductions, yet these appropriate reductions lengthened treatment. In contrast, the DP arm included fewer patients who were able to continue treatment, despite the lower proportion of dose reductions and skipped treatments. We believe that declining QOL was an important cause of treatment discontinuation in the DP arm.

The toxicity profiles also differed between the two arms. In the docetaxel arm, neutropenia was most prominent, and grade 4 neutropenia occurred in up to 68% of the patients. Consequently, febrile neutropenia was observed in 15% of the patients in the docetaxel arm, whereas no patients experienced febrile neutropenia in the DP arm. The frequency of febrile neutropenia in the docetaxel arm was similar to that seen in a previous Japanese docetaxel study for elderly patients.[5] However, because febrile neutropenia was successfully managed with appropriate supportive treatments, there were no treatment-related deaths in the docetaxel arm. However, the DP arm had higher incidences of grade $\geq$ 3 anemia, hyponatremia, and anorexia. We suppose that these were the main causes of the decline in the QOL score in the DP arm. The median number of treatment cycles and the proportion of patients in whom treatment could be continued for five or more cycles in the DP arm were smaller than those in the docetaxel arm. These findings could be associated with the decline in QOL and might have affected OS in the DP arm. Three of four treatment-related deaths in the DP arm were caused by pneumonitis. It was reported that weekly docetaxel administration increases the frequency of pneumonitis.[21,22] In this study, there were few differences in the frequencies of pneumonitis between the two arms; however, more severe pneumonitis was observed in the DP arm.

Quoix et al[18] demonstrated the superiority of carboplatin plus weekly paclitaxel over conventional standard therapy, namely vinorelbine or gemcitabine monotherapy, in the Intergroupe Francophone de Cancerologie Thoracique 0501 study. The usefulness of platinum-based treatments in elderly patients was first shown in a prospective study. For elderly patients with NSCLC, carboplatin combination therapy may be preferable to a split cisplatin combination. However, the high incidence of toxicity could not be ignored, because treatment-related deaths occurred in 4.4% of patients in the doublet arm but only in 1.3% of patients in the monotherapy arm.[18] In contrast, a phase I trial of combined carboplatin plus pemetrexed (PEM), followed by maintenance PEM, showed good tolerability in elderly patients with nonsquamous NSCLC.[23] We consider that the combination of carboplatin plus PEM should be compared with docetaxel monotherapy.

In conclusion, this study failed to demonstrate any advantages of weekly DP over docetaxel monotherapy as first-line chemotherapy for elderly patients with advanced NSCLC, and docetaxel every 3 weeks remains the standard treatment for elderly patients with advanced NSCLC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. 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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Manuscript writing: All authors
Final approval of manuscript: All authors

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GLOSSARY TERMS

cisplatin: an inorganic platinum agent (cis-diamminedichloroplatinum) with antineoplastic activity. Cisplatin forms highly reactive, charged, platinum complexes, which bind to nucleophilic groups such as GC-rich sites in DNA, inducing intrastrand and interstrand DNA cross-links as well as DNA-protein cross-links. These cross-links result in apoptosis and cell growth inhibition. Carboplatin and oxaliplatin are other members of this class.

docetaxel: a member of the taxane group of antimitotic chemotherapy medications whose mode of action is to bind and stabilize microtubules and thus disrupt cell division.

non–small-cell lung cancer (NSCLC): a type of lung cancer that includes squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma.

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Appendix

Reasons for Bolus Cisplatin Administration Unsuitability

Patients age 70 to 74 years were examined before enrollment for the following six conditions, which defined them as unsuitable for bolus cisplatin administration (Appendix Table A1): a combination of more than one mild organ dysfunction, but violating none of the inclusion criteria; a combination of comorbid illness and mild organ dysfunction, but violating none of the inclusion criteria; organ dysfunction not specified by the inclusion/exclusion criteria; a combination of more than one comorbid illness; a comorbid illness not specified by the exclusion criteria; or any other condition.

Procedures of Administration

In the docetaxel monotherapy arm, docetaxel was diluted with 250 to 500 mL of 5% glucose solution or physiologic saline and administered by intravenous infusion over 60 minutes.

In the docetaxel plus cisplatin (DP) arm, docetaxel was diluted with 250 mL of 5% glucose solution or 200 mL of physiologic saline and administered by intravenous infusion over 60 minutes. Cisplatin was administered by intravenous infusion over 15 to 20 minutes, directly or after being diluted with physiologic saline, after docetaxel administration. A total of 1,000 to 1,500 mL of fluid was administered before and after the administration of cisplatin. During treatment with cisplatin, careful attention was paid to urinary output, and diuretics such as mannitol and furosemide were administered if necessary. Antiemetics such as 5-hydroxytryptamine-3 receptor antagonists and steroids were also administered if necessary.

Dose Reduction Criteria and Methods

In both arms, the presence of grade 4 neutropenia, febrile neutropenia, or grade $\geq$ 3 nonhematologic toxicity (except anorexia, nausea, vomiting, hyponatremia, constipation, and hyperglycemia) necessitated dose reduction (docetaxel arm levels -1 and -2: docetaxel 50 and 40 mg/m^2, respectively; DP arm level -1: docetaxel 15 mg/m^2 and cisplatin 20 mg/m^2). In addition, if serum creatinine levels exceeded 2.0 mg/dL, the administration of cisplatin was stopped in subsequent cycles in the DP arm. The persistence of these toxicities after two dose-reduction steps in the docetaxel arm or one dose-reduction step of each drug in the DP arm prompted treatment discontinuation.

Definition of Overall and Progression-Free Survival

Overall survival was measured from the date of random assignment to death from any cause and was censored at the last follow-up date. Progression-free survival was measured from the date of random assignment to the first observation of disease progression or death from any cause if there was no progression. If there was no progression and the patient did not die, progression-free survival data were censored at the date on which the absence of progression was confirmed.

Table A1. Conditions Defining Patients As Unsuitable for Bolus Cisplatin Administration

Condition	No. of Patients	
	Docetaxel (n = 31)	Docetaxel/Cisplatin (n = 32)
Combination of more than one mild organ dysfunction, but violating none of the inclusion criteria	6	4
Combination of comorbid illness and mild organ dysfunction, but violating none of the inclusion criteria	5	8
Organ dysfunction not specified by the inclusion/exclusion criteria	8	3
Combination of more than one comorbid illness	1	7
Comorbid illness not specified by the exclusion criteria	2	2
Any other condition	9	8

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Clinical Trial Note

OXFORD

Clinical Trial Note

A Phase II/III study comparing carboplatin and irinotecan with carboplatin and etoposide for the treatment of elderly patients with extensive-disease small-cell lung cancer (JCOG1201)

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Abstract

A randomized Phase II/III trial commenced in Japan in December 2013. Carboplatin plus etoposide is the current standard treatment for elderly extensive-disease small-cell lung cancer. The purpose of this study is to confirm the superiority of carboplatin plus irinotecan in terms of overall survival over carboplatin plus etoposide for elderly extensive-disease small-cell lung cancer patients in a Phase II/III design. A total of 370 patients will be accrued from 38 Japanese institutions within 5 years. In the Phase II part, the primary endpoint is the response rate of the carboplatin plus irinotecan arm and the secondary endpoint is adverse events. In the Phase III part, the primary endpoint is overall survival and the secondary endpoints are progression-free survival, response rate, adverse events, serious adverse events and symptom score. This trial has been registered at the UMIN Clinical Trials Registry as UMIN000012605 (http://www.umin.ac.jp/ctr/index.htm).

Key words: small-cell lung carcinoma, extensive-disease, elderly, chemotherapy, Phase II/III

Introduction

Lung cancer is the leading cause of cancer-related deaths in Japan (1). Approximately 70% of lung cancer-related deaths occur in patients aged 70 years or older (1). Small-cell lung cancer (SCLC) accounts for 13–15% of all lung cancers and 60–70% of these patients present with extensive disease (ED) (2).

The standard treatment for extensive-disease small-cell lung cancer (ED-SCLC) is combination chemotherapy including a platinum agent, which is a key drug for SCLC. Cisplatin is widely used in non-elderly patients, but causes severe renal and gastrointestinal toxicities. Therefore, the Lung Cancer Study Group of the Japan Clinical Oncology Group (JCOG) previously conducted a Phase III trial (JCOG9702) and evaluated the efficacy and safety of carboplatin,

which is known to cause milder renal and gastrointestinal toxicities than cisplatin.

JCOG9702 was a Phase III trial that compared split doses of cisplatin plus etoposide (SPE) and carboplatin plus etoposide (CE) in elderly or poor-risk patients with ED-SCLC. The CE regimen consisted of four courses of carboplatin, area under the curve (AUC) 5, on Day 1 and etoposide 80 mg/m^2/day on Days 1–3, repeated every 3–4 weeks. The SPE regimen consisted of four courses of cisplatin 25 mg/m^2/day on Days 1–3 and etoposide 80 mg/m^2/day on Days 1–3, repeated every 3–4 weeks. Survival curves almost overlapped (median survival of 9.9 months versus 10.6 months, $P = 0.54$) and most of the toxicities observed were equivalent (3). Based on these results and the usefulness of carboplatin, which did not require hydration and was easily administered in an outpatient setting, the JCOG Lung Cancer Study Group concluded that CE should be the standard regimen for elderly ED-SCLC.

In 2002, JCOG9511 demonstrated the superiority of irinotecan over etoposide in combination with cisplatin for the treatment of ED-SCLC patients who were 70 years or younger. This was a randomized Phase III trial that planned to accrue 230 patients and terminated early after accruing 154 patients because an interim analysis showed overall survival was significantly longer in the irinotecan plus cisplatin (IP) arm than in the etoposide plus cisplatin (EP) arm (12.8 months versus 9.4 months, $P = 0.002$ by the log-rank test) (4). Although three randomized controlled trials conducted after the JCOG9511 study failed to reproduce the superiority of IP (5–7), a meta-analysis suggested that IP may be superior to EP in terms of overall survival with less hematological toxicities (8). Therefore, the introduction of irinotecan in the treatment of elderly patients with ED-SCLC is expected to produce promising results.

Misumi et al. (9) conducted a feasibility study of carboplatin plus irinotecan (CI) for elderly ED-SCLC patients at six institutions in Japan to determine the optimal dose. Four courses of carboplatin (AUC = 4 mg/ml × min, Day 1) and irinotecan (50 mg/m^2/day, Days 1 and 8) repeated every 3 weeks was chosen as the study regimen based on the previously reported Phase I study for LD-SCLC (10). Ten patients were enrolled and all of them completed the planned three courses without dose reductions. Responses were observed in 9 out of 10 patients. Although no Grade 4 adverse events occurred, prolonged hematological toxicities were observed. Therefore, further dose escalations were judged to be infeasible, and carboplatin (AUC = 4 mg/ml × min, Day 1) and irinotecan (50 mg/m^2/day, Days 1 and 8) repeated every 3 weeks was determined to be the optimal regimen for elderly patients.

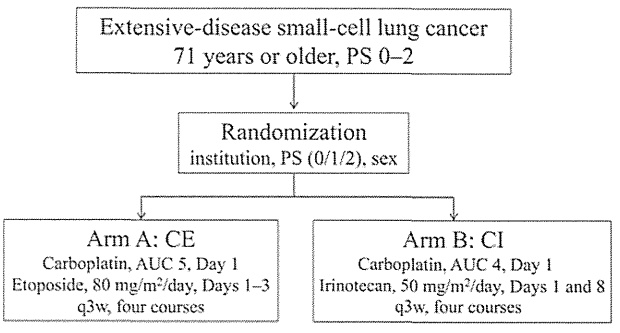

Figure 1. Schema of the study. PS, performance status; AUC, area under the curve.

Two randomized Phase III trials that compared CE versus CI for ED-SCLC including both elderly and non-elderly patients were conducted in Europe. Although Schmittel et al. (11) reported no significant differences in overall survival between CE and CI (9.0 months versus 10.0 months, $P = 0.06$), Hermes et al. (12) demonstrated that CI was superior to CE (7.1 months versus 8.5 months, $P = 0.02$). Grade 3 or 4 hematological toxicities were similar between the arms or milder in CI, whereas diarrhea was more frequent in CI in both studies.

Based on these backgrounds, we commenced a multicenter randomized Phase II/III trial to confirm the superiority of CI in terms of overall survival over CE for elderly ED-SCLC patients (Fig. 1).

The JCOG Protocol Review Committee approved this study protocol in November 2013 and patient enrollment began in December 2013. Approval was obtained from the Institutional Review Board prior to starting patient accrual at each institution. This trial has been registered at the UMIN Clinical Trials Registry as UMIN000012605 (http://www.umin.ac.jp/ctr/index.htm).

Protocol digest of the JCOG1201

Objectives

The purpose of this study is to confirm the superiority of CI in terms of overall survival (OS) over CE in elderly patients with ED-SCLC in Phase II/III design.

Study setting

A multi-institutional two-arm open label randomized Phase II/III study.

Endpoints

The primary endpoint and secondary endpoint in the Phase II part is the response rate in the CI arm and adverse events, respectively. The primary endpoint in the Phase III part is OS in all randomized patients. OS is defined as days from randomization to death from any cause, and is censored at the last day when the patient is alive. The secondary endpoints in the Phase III part are progression-free survival (PFS), response rate, adverse events, serious adverse events and the symptom score. PFS is defined as days from randomization to progression or death from any cause, and is censored at the last day when the patient is alive without any evidence of progression.

Eligibility criteria

Inclusion criteria

1. Histologically or cytologically confirmed SCLC.
2. Extensive disease diagnosed with enhanced chest CT, enhanced cranial CT or MRI, enhanced upper abdominal CT or ultrasound, bone scintigraphy or FDG-PET.
3. No serious tumor-related complications such as superior vena cava syndrome, massive or uncontrollable pleural or cardiac effusion, or symptomatic brain metastasis.
4. Aged 71 years or older.
5. ECOG performance status of 0–2.
6. With measurable lesions.
7. No prior surgery, radiotherapy or chemotherapy for SCLC.
8. No prior thoracic radiotherapy or chemotherapy for any other cancers.
9. Adequate organ functions.
10. No diarrhea or intestinal obstruction.
11. Written informed consent.

Exclusion criteria

1. Synchronous or metachronous (within 5 years) malignancies, except for carcinoma *in situ* or mucosal tumors curatively treated with local therapy.
2. Active infection requiring systemic therapy.
3. Body temperature 38°C.
4. Severe mental disease.
5. Patients receiving systemic steroid medication.
6. Poorly controlled diabetes mellitus or receiving the routine administration of insulin.
7. Poorly controlled hypertension.
8. Unstable angina within 3 weeks or a history of myocardial infarction within 6 months.
9. Interstitial pneumonia, pulmonary fibrosis or severe emphysema.

Randomization

After confirming the eligibility criteria, registration is made by a web-based system to the JCOG Data Center. Patients are randomized to either the CE arm or CI arm by the minimization method balancing the arms with the institution, ECOG performance status (0 versus 1 versus 2), and sex (male versus female).

Treatment methods

Patients in the CE arm receive four courses of CE (carboplatin, AUC 5, Day 1; etoposide, 80 mg/m^2/day, Day 1–3) repeated every 3 weeks. Patients in the CI arm receive four courses of CI (carboplatin, AUC 4, Day 1; irinotecan, 50 mg/m^2/day, Day 1, 8) repeated every 3 weeks. When the leukocyte count is decreased to <3000/mm^3 or the platelet count to <100 000/mm^3 on the planned first day of both arms, the start of chemotherapy is delayed until the counts recover to ≥3000/mm^3 and ≥100 000/mm^3, respectively. The administration of irinotecan is skipped on Day 8 when at least one of the following occurs; a leukocyte count <3000/mm^3, platelet count <100 000/mm^3, diarrhea Grade 1 or higher, or a fever of ≥38°C. The dose of etoposide and irinotecan in the subsequent cycles is reduced by 20 and 10 mg/m^2 from the planned dose, respectively, when the leukocyte count is <1000 mg/m^3, platelet count is <25 000/mm^3 and/or Grade 3 non-hematologic toxicities (excluding nausea, vomiting, hyponatremia, anorexia and increased creatinine levels) develop. The dose of carboplatin is reduced to AUC 4 in the CE arm when patients have a leukocyte count <1000 mg/m^3, platelet count <25 000/mm^3 and/or Grade 3 non-hematologic toxicities (excluding nausea, vomiting, hyponatremia, anorexia and increased creatinine levels). The dose of carboplatin in the CI arm is not modified. The protocol treatment is terminated when patients exhibit Grade 4 non-hematologic toxicities. After completion of the protocol treatment, patients are observed without anti-cancer treatment including prophylactic cranial irradiation until recurrence is detected. Crossover is allowed in both arms after the termination of the protocol treatment or at the time of progression.

Follow-up

All randomized patients are followed-up for at least 1.5 years after patient accrual is completed. Enhanced chest CT and tests for tumor markers (CEA, NSE and ProGRP) are performed during the second and fourth courses to evaluate responses. Enhanced computed tomography of the upper abdomen and enhanced computed tomography or enhanced MRI of the brain are also performed during the second and fourth courses when patients have lesions in the examined regions at baseline. Bone scintigraphy or fluorodeoxyglucose-positron emission tomography is performed when progression is suspected. Chest X-rays, complete blood counts and chemistries are performed every month for the first year, every 3 months for the second year, and every 6 months afterwards.

Study design and statistical analysis

This randomized Phase II/III trial is designed to confirm the superiority of CI in terms of overall survival over CE for elderly ED-SCLC patients. The Phase II part is incorporated to confirm if CI has adequate efficacy to proceed to the Phase III part because there have been few studies to support the efficacy of CI for elderly ED-SCLC patients.

In the Phase II part, the planned sample size is 48 patients in the CI arm, which was calculated based on an expected response rate of 65% and a threshold of 45%, with a one-sided alpha of 0.1 and a beta of 0.1.

In the Phase III part, we assumed the median survival time with CE to be 11.0 months, and expected a 3.5-month increase in the median survival time with CI based on the result of JCOG9511. According to Schoenfeld and Richter's method (13), the sample size was calculated as 183 patients per arm with a one-sided alpha level of 5%, a power of 80%, an accrual period of 5 years, a follow-up period of 1.5 years, and 324 expected events in total. The total sample size was set at 370 patients to account for patients lost to follow-up. All statistical analyses will be conducted at the JCOG Data Center.

Interim analysis and monitoring

We plan to conduct two interim analyses. The first interim analysis will be conducted as the analysis of Phase II part to determine whether to proceed to the Phase III part after the pre-planned accrual of the Phase II part, the first 48 patients in CI arm, is completed. The second interim analysis with a comparison between the arms will be conducted after half of the planned number of patients in the Phase III part is enrolled. The Lan–DeMets method with the O'Brien and Fleming type alpha spending function will be used to adjust multiplicity of the second interim analysis and the primary analysis (14).

The Data and Safety Monitoring Committee (DSMC) of the JCOG will review the interim analysis reports independently from the group investigators and group statistician. If the superiority of the CI arm is demonstrated in the second interim analysis with a one-sided *P* value of the stratified log-rank test below an adjusted alpha level, the study will be terminated.

In-house monitoring will be performed every 6 months by the JCOG Data Center to evaluate and improve study progress, data integrity and patient safety.

Participating institutions (from North to South)

Asahikawa Medical Center, National Hospital Organization Hokkaido Cancer Center, KKR Sapporo Medical Center, Miyagi Cancer Center, Yamagata Prefectural Central Hospital, Ibaraki Prefectural Central Hospital and Cancer Center, Tochigi Cancer Center, National Nishigunma Hospital, Gunma Prefectural Cancer Center, Saitama Cancer Center, National Cancer Center Hospital East, National Cancer Center Hospital, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, National Center for Global Health and Medicine (NCGM), Cancer Institute Hospital of Japanese Foundation for Cancer Research, Juntendo University Hospital, Kanagawa Cancer Center, Yokohama Municipal Citizen's Hospital, Niigata Cancer Center Hospital, Gifu Municipal Hospital,

Shizuoka Cancer Center, Aichi Cancer Center Hospital, National Hospital Organization Nagoya Medical Center, Aichi Cancer Center, Aichi Hospital, Osaka City University Hospital, Kinki University Faculty of Medicine, Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka Prefectural Hospital Organization Osaka Prefectural Medical Center for Respiratory and Allergic Disease, National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka City General Hospital, Hyogo Cancer Center, Institute of Biomedical Research and Innovation Hospital, Kurashiki Central Hospital, Okayama University Hospital, National Hospital Organization Yamaguchi-Ube Medical Center, National Hospital Organization Shikoku Cancer Center, National Kyushu Cancer Center, and Kumamoto Regional Medical Center Hospital.

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Conflict of interest statement

None declared.

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ORIGINAL ARTICLE

Phase II study of carboplatin, docetaxel and bevacizumab for chemotherapy-naïve patients with advanced non-squamous non-small cell lung cancer

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Abstract
Purpose To evaluate a 3-drug combination of carboplatin, docetaxel and bevacizumab as a front-line chemotherapy for patients with advanced non-squamous non-small cell carcinoma (NSCLC), a single arm phase II study was conducted.
Methods Patients with stage IIIB/IV or postoperative recurrent non-squamous NSCLC were treated with carboplatin (targeted area under the curve of 6 mg h/L), docetaxel (60 mg/m^2), and bevacizumab (15 mg/kg) on day 1, repeated every 3 weeks for 4 to 6 cycles, followed by maintenance with bevacizumab every 3 weeks until disease progression or occurrence of predefined toxicity. The planned patient number was 40, and the primary endpoint was progression free survival (PFS) as assessed by independent reviewers.
Results One patient refused the treatment after enrollment; thus, 39 patients were treated and analyzed. The 3-drug therapy was delivered for a median of 4 cycles,

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and 54 % of the patients proceeded to the maintenance therapy for a median of 4 cycles. The overall response rate was 74.4 % (29/39), with a 95 % confidence interval (CI) of 60.0 to 88.7 %. The median PFS and overall survival (OS) were 6.2 months (95 % CI, 4.8–8.5 months) and 22.4 months (95 % CI, 11.3–26.2 months), respectively. Toxicities of grade 3 or higher included neutropenia in 71.8 %, febrile neutropenia in 23.1 %, and hypertension in 38.5 % of the patients, but they were transient and manageable.

Conclusion The primary endpoint was met. The regimen yielded promising results with an excellent overall response rate, PFS, and OS for chemotherapy-naïve patients with advanced non-squamous NSCLC. Further studies are warranted.

Keywords Non-squamous · Non-small cell lung carcinoma · Bevacizumab · Docetaxel · Carboplatin · Phase II study

Introduction

The standard front-line therapy for advanced non-small cell lung cancer (NSCLC) has been a platinum-based two-drug combination chemotherapy administered for 4 to 6 cycles [1–4]. Several alternatives, however, are currently available in addition to the two-drug combination chemotherapy for advanced non-squamous cell NSCLC. For patients with tumors harboring a driver mutation such as epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK)-fusion gene, treatment with a corresponding tyrosine kinase inhibitor (TKI) is regarded as a standard front-line therapy because of the improved progression-free survival (PFS) time, quality of life (QOL), and toxicity characteristics over the conventional platinum-based combination chemotherapy [5–11]. Other options for the treatment of advanced non-squamous NSCLC in a front-line setting include the addition of bevacizumab to the standard platinum-based combinations [12–14] or maintenance therapy with pemetrexed [15]. Regarding bevacizumab, a regimen consisting of carboplatin and paclitaxel combined with the simultaneous and maintenance administration of bevacizumab was compared with conventional chemotherapy consisting of carboplatin and paclitaxel [12]. In this trial, the additional and maintenance use of bevacizumab significantly prolonged the PFS and OS over the conventional regimen, whereas another phase III study evaluating the role of bevacizumab combined with another regimen consisting of cisplatin and gemcitabine prolonged the PFS, compared with that for conventional chemotherapy, but had no significant prolongation of the OS [14].

Despite the use of a variety of agents, including pemetrexed, docetaxel, paclitaxel, nab-paclitaxel, gemcitabine, vinorelbine, irinotecan, and S-1, as a counterpart to a platinum agent, no concrete evidence supporting the superiority of a specific agent exists. Nevertheless, only docetaxel and pemetrexed have been included as standard chemotherapeutic agents in both front-line and second-line settings for advanced non-squamous NSCLC. Docetaxel combined with cisplatin was proven to be significantly superior, in terms of OS, over vindesine combined with cisplatin in a front-line setting for NSCLC [3]. Docetaxel was also proven to prolong the OS significantly, compared with best-supportive care alone, in a second-line setting for NSCLC [16]. On the other hand, pemetrexed combined with cisplatin was proven to be non-inferior to gemcitabine and cisplatin in a front-line therapy for NSCLC; however, subset analyses of the study revealed that pemetrexed was clinically relevant only for non-squamous NSCLC [17, 18]. Furthermore, pemetrexed monotherapy was shown to be equivalent to docetaxel monotherapy for patients with non-squamous NSCLC in a second-line setting [19]. Taken together, a regimen with cisplatin combined with one of docetaxel or pemetrexed might be the most evidence-based front-line regimen available for advanced non-squamous NSCLC. A combination consisting of docetaxel and cisplatin as the control regimen in a front-line setting exhibited an excellent OS of as long as 37.3 months, even for EGFR mutation positive NSCLC [6, 20].

Regarding platinum agents, a meta-analysis revealed a modest but statistically significant superiority of cisplatin over carboplatin in terms of OS [21]. In addition, other meta-analysis using individual patient data [22] disclosed superior OS with cisplatin to OS with carboplatin in patients with non-squamous NSCLC. Fossella et al. [23] conducted a randomized study comparing a combination chemotherapy consisting of docetaxel and either cisplatin or carboplatin with a former standard regimen consisting of cisplatin and vinorelbine with the primary endpoint of OS. In this study, the combination of cisplatin and docetaxel demonstrated statistically significantly prolonged OS over the combination of cisplatin and vinorelbine, whereas the combination of carboplatin and docetaxel failed to do that. On the other hand, both combinations of cisplatin plus docetaxel and carboplatin plus docetaxel provided better QOL than cisplatin and vinorelbine. These results provide further evidence that combination regimens of platinum and docetaxel should be new standard first-line regimens for advanced NSCLC, and that the combination with cisplatin is better than the combination with carboplatin in terms of OS. Despite such evidence, carboplatin is often preferred to cisplatin because of the latter's association with nuisance toxicities such as nausea, vomiting, and renal dysfunction that require the extensive prophylactic use of antiemetics and massive hydration. Therefore, we hypothesized that the addition of bevacizumab to the induction and maintenance phases might overcome the small disadvantage

of replacing cisplatin with carboplatin in combination chemotherapy consisting of docetaxel and cisplatin for advanced non-squamous NSCLC. Thus, a phase II study of combination chemotherapy with carboplatin, docetaxel, and bevacizumab for advanced non-squamous NSCLC was conducted to test this hypothesis.

Patients and methods

Patients

Patients meeting all of the following criteria were enrolled in this multicenter trial: (i) histologically or cytologically confirmed non-squamous NSCLC of clinical stage IIIB/IV (according to the UICC – 7th version) or recurrent disease after surgery for which curative-intent thoracic radiotherapy was not indicated; (ii) chemotherapy-naïve (postoperative and/or induction chemotherapy were not allowed, whereas postoperative adjuvant chemotherapy with uracil and tegafur (UFT) alone was allowed); (iii) a performance status (PS, Eastern Cooperative Oncology Group) of 0–1; (iv) an age between 20 and 74 years; (v) adequate organ functions (neutrophils $\geq$1,500/mm^3, platelets $\geq$100,000/mm^3, hemoglobin $\geq$9.0 g/dL, total bilirubin $\leq$ upper normal limit (UNL) $\times$ 1.5, AST/ALT $\leq$ UNL $\times$ 2.5, creatinine clearance $\geq$45 mL/min, SpO_2 $\geq$93 %, proteinuria $\leq$(1+) or 2 g/24 h); (vi) measureable lesions using response evaluation criteria in solid tumors (RECIST) version 1.1; (vii) defined intervals from previous treatments when applicable ($\geq$2 weeks from palliative radiotherapy excluding thoracic irradiation, $\geq$4 weeks from major surgery for any purpose, $\geq$2 weeks from pleural or pericardial drainage, $\geq$2 weeks from open biopsy for any lesion, central-venous port installation, treatment for any external injury, $\geq$1 week from aspiration biopsy, and $\geq$6 months from postoperative adjuvant chemotherapy with UFT); (viii) life expectancy exceeding 3 months; and (ix) written informed consent. Patients with any of the following conditions were not eligible: (i) serious complications including heart failure, uncontrolled infection, uncontrolled hypertension, interstitial pneumonia/pulmonary fibrosis detectable on computed tomography (CT) scan; (ii) serious previous medical conditions, including gastrointestinal perforation, within the last 1 year, other synchronous or metachronous malignancies within the last 5 years, myocardial infarction, cerebral infarction, drug-induced interstitial pneumonia, or psychological diseases; (iii) massive pleural effusion or ascites; (iv) untreated brain metastasis; (v) the use of anticoagulants (except for aspirin with a dose $\leq$324 mg/day); (vi) current or previous history of hemoptysis of $\geq$2.5 mL lasting for $\geq$1 week or requiring any hemostatic agents; (vii) obvious cavitation in the tumor; (viii) tumor invasion to large vessels; (ix) any scheduled surgery during the study period; (x) current pregnancy or breast-feeding; and (xi) any other conditions investigators judged as being inappropriate for enrollment.

Evaluation

The baseline evaluation included a history with a complete record of concomitant medical conditions, physical examinations, PS, complete blood counts, serum chemistries and electrolytes, urinalysis, chest radiogram, chest CT, abdominal CT, brain magnetic resonance imaging with contrast medium enhancement unless otherwise contraindicated, and a bone scintigram which could be substituted with positron-emission tomography-CT. All of these examinations were performed within 1 month prior to enrollment.

During chemotherapy, each patient's symptoms, physical examination, complete blood counts, serum chemistries and urinalysis were monitored at least once a cycle. Toxicity was evaluated for every course according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Chest CT and other radiographic modalities necessary for evaluating target lesions using the RECIST, were repeated every 6 weeks until evidence of disease progression. The tumor response in each patient was evaluated by external reviewers according to the RECIST 1.1, and the response was classified into 5 categories: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) and not evaluable (NE). A minimum of a 6-week interval from the start of therapy was required to establish SD.

Drug administration

The chemotherapy consisted of docetaxel at a dose of 60 mg/m^2, carboplatin at a dose corresponding to a target area under the curve (AUC) of 6 mg h/L calculated using the Calvert's formula, and bevacizumab at a dose of 15 mg/kg on day 1. This regimen was repeated every 3 weeks for at least 4 cycles and up to 6 cycles (induction phase), followed by maintenance treatment with bevacizumab repeated every 3 weeks (maintenance phase) until disease progression unless predefined dose-reduction or stopping criteria were encountered. Although not mandatory, the use of granulocyte colony-stimulating factor was allowed at the discretion of the treating investigators and according to the approved conditions in Japan (grade 4 neutropenia or febrile neutropenia). Post-treatment therapy was withheld until evidence of disease progression, with no restrictions thereafter.

Dose reduction and termination criteria for chemotherapy

On day 1 of each cycle, the treatment was postponed until recovery when any of the following conditions were

encountered: neutropenia (<1,500/mm^3), thrombocytopenia (<75,000/mm^3), elevated transaminases (AST or ALT >2.5 × UNL), elevated serum creatinine (>1.5 mg/dL), decreased creatinine clearance (<45 mL/min), proteinuria (≥2+), hypertension (≥grade 3) and other non-hematological toxicities (≥grade 3), except for hair loss, nausea/vomiting, appetite loss and asthenia. The dose of docetaxel or carboplatin was reduced if any of the following conditions were encountered: grade 4 neutropenia, febrile neutropenia, thrombocytopenia (≥grade 3), elevated AST or ALT (≥grade 3), or peripheral neuropathy (≥grade 2). For the first step in dose reduction, only docetaxel was reduced to 50 mg/m^2, with the carboplatin dose unaltered. For the second step, the dose of carboplatin was reduced to AUC = 5, with the docetaxel dose maintained at 50 mg/m^2. For the third step, the dose of docetaxel was reduced to 40 mg/m^2, with the carboplatin dose maintained at AUC = 5. For the fourth and final step, the dose of carboplatin was reduced to AUC = 4, with the docetaxel dose maintained at 40 mg/m^2. Bevacizumab dose reduction was not allowed. The treatment was entirely terminated when further dose reductions were required, when treatment was postponed for more than 3 weeks, or when any of the following conditions were observed: hemoptysis (≥grade 2), other types of bleeding (≥grade 3), disease progression, patient refusal, or other conditions that the investigators judged as being inadequate to allow continued treatment.

Statistical and ethical considerations

The primary endpoint of the study was PFS, as assessed by independent reviewers according to the RECIST version 1.1. The secondary endpoints were the overall response rate (ORR), as assessed by independent reviewers according to the RECIST version 1.1, OS, and safety. As we hypothesized that the addition of bevacizumab might overcome the potential shortcoming of substituting cisplatin with carboplatin, the PFS in three previously published studies [2, 24, 25] examining docetaxel and cisplatin were consulted. As the reported PFS were 3.7 months [2], 4.3 months [25], and 5.0 months [24], respectively, we estimated the PFS of the regimen as being 4.6 months. On the other hand, the PFS of a phase II study with paclitaxel, carboplatin, and bevacizumab that was conducted in Japan was 6.9 months [26]. Therefore, a target PFS of 7.0 months and a threshold PFS of 4.6 months were used to calculate the sample size. With α and β errors of 0.05 and 0.20, respectively, the calculated minimum sample size was 37 patients, with enrollment and follow-up periods of 1.0 and 1.5 years, respectively. Then, a final sample size of 40 was selected. The study was conducted as a cooperative study involving 8 institutions belonging to the Tokyo Cooperative Oncology Group (TCOG) and was approved by the institutional review boards of each institution. The study was registered in the clinical trial registration system of the University Hospital Medical Information Network Clinical Trials Registry (identification number, UMIN000004524) on November 11, 2010.

Results

Patient characteristics

From December 2010 to February 2012, 40 patients were enrolled; one patient subsequently refused the treatment after enrollment and before the start of treatment. Therefore, the remaining 39 patients were analyzed for survival and toxicity. The patient characteristics of the 39 patients are listed in Table 1.

Treatment delivery, dose reduction and toxicity

Treatment was terminated because of toxicities in 17 patients (44 %), including 10 patients who did not proceed to the maintenance therapy with bevacizumab. In the

Table 1 Baseline characteristics of the patients ($n = 39$)

Age (years)	
Median (range)	62 (36–73)
Gender, *n* (%)	
Female	12 (31)
Male	27 (69)
PS (ECOG), *n* (%)	
0	26 (67)
1	13 (33)
Smoking, *n* (%)	
Current smoker	15 (38)
Ex smoker	11 (28)
Never smoker	13 (33)
Histology, *n* (%)	
Adenocarcinoma	36 (92)
NOS	3 (8)
Stage, *n* (%)	
IIIB	0
IV	36 (92)
Post operative	3 (8)
EGFR mutation, *n* (%)	
Wild	31 (79)
Mutant	5 (13)
Unknown	3 (8)

NOS not otherwise specified, non-squamous NSCLC; *PS* performance status; *ECOG* Eastern Cooperative Oncology Group; *EGFR* epidermal growth factor receptor

induction phase, the 3-drug combination was delivered for a median of 4 cycles ($n = 39$, ranging from 1 to 6 cycles), and 21 patients (54 %) proceeded to the maintenance phase, receiving a median of 4 cycles (range 2 to 30).

Among the 39 patients, 3 patients received only one cycle. Among the remaining 36 patients, one-step, two-step, three-step, and four-step dose reductions were performed because of toxicities in 10 (28 %), 5 (14 %), 3 (8 %), and 3 (8 %) patients, respectively, during the entire course of treatment. The adverse events are listed in Table 2. Although manageable, neutropenia ≥grade 3 occurred in 71.8 % of the patients, with febrile neutropenia in 23.1 %. Hypertension ≥grade 3 was observed in 38.5 % of the patients. All the other events were infrequent and mild. No treatment-related deaths occurred in this series.

Response rate

External reviews by independent reviewers established an ORR of 74.4 % (29/39) with a 95 % confidence interval (CI) ranging from 60.0 to 88.7 % and a disease control rate of 94.9 % (37/39; 95 % CI, 87.6–100 %), including no CR, PR in 29 patients, SD in 8 patients, PD in 1 patient, and NE in 1 patient. The best response for target lesions in each patient was shown in a waterfall plot (Fig. 1).

Post-treatment and survival

Of the 39 patients, 30 (77 %) patients underwent second-line chemotherapy. Nine (23 %) and 11 (28 %) patients were treated with a platinum-containing regimen and EGFR-TKIs, respectively. After completing the study, 2 patients were shown to carry an ALK fusion gene in the tumor and were treated with crizotinib. Seventeen patients (44 %) were treated with multiple regimens as post-treatment.

At the completion of the study follow-up, disease progression had not occurred in 2 patients, and these patients were censored in the PFS analysis. At a median follow-up period of 20.0 months (range 1.6–33.5), 13 (33.3 %) patients were still alive, and they were censored in the OS analysis. The median PFS and median OS times were 6.2 months (95 % CI, 4.8–8.5) and 22.4 months (95 % CI, 11.3–26.2), respectively. The 1-year and 2-year survival rates with standard deviations were 64.1 ± 7.7 % and 44.4 ± 8.3 %, respectively. Figure 2a, b shows the Kaplan–Meier curves for the PFS and OS, respectively. When limited to patients with tumors of EGFR mutation ($n = 5$), the median PSF and median OS times were 7.9 and 33.2 months, respectively. The PFS times of two patients with tumors with the ALK fusion gene were 5.8

Table 2 Adverse events during the entire treatment including any event of ≥grade 3 ($n = 39$)

	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	≥Grade 3 (%)
Hematological					
Anemia	30.8	20.5	12.8	0	12.8
Leucocytopenia	7.7	25.6	38.5	17.9	56.4
Neutropenia	5.1	12.8	10.3	61.5	71.8
Thrombocytopenia	46.2	15.4	7.7	2.6	10.3
Febrile neutropenia	–	–	23.1	0	23.1
Non-hematological					
Hypoalbuminemia	28.2	17.9	2.6	0	2.6
ALP increased	17.9	2.6	2.6	0	2.6
Hyponatremia	20.5	0	2.6	2.6	5.1
Hyperkalemia	17.9	2.6	5.1	0	5.1
Proteinuria	5.1	23.1	2.6	0	2.6
Hypertension	7.7	25.6	38.5	0	38.5
Diarrhea	20.5	12.8	2.6	0	2.6
Appetite loss	48.7	12.8	10.3	0	10.3
Nausea	33.3	20.5	5.1	0	5.1
Constipation	41.0	2.6	2.6	0	2.6
Fatigue	20.5	12.8	2.6	0	2.6
Infection	0	12.8	2.6	0	2.6
Mucositis	23.1	5.1	2.6	0	2.6
Tumor pain	0	2.6	2.6	0	2.6
Ileus	0	0	2.6	0	2.6
Chorecystitis	0	0	2.6	0	2.6

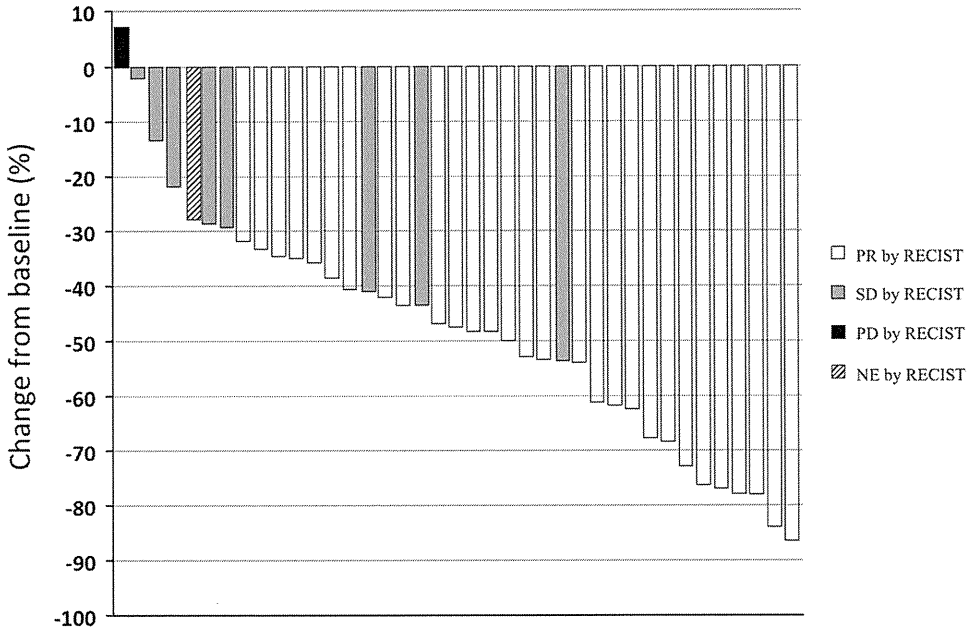

Fig. 1 A waterfall plot analysis showing the best change in the longest diameter, compared with the baseline measurement, in each patient. The *open*, *gray*, *closed*, and *shaded bars* represent a partial response, stable disease, progressive disease, and not evaluable, respectively, according to the RECIST 1.1 criteria. No complete responses were observed in this study

and 15.5 months, respectively: these two patients were still alive at the termination of the follow up.

Discussion

In this study, a three-drug combination chemotherapy consisting of carboplatin (AUC = 6), docetaxel (60 mg/m^2, the standard dose for the treatment of NSCLC in Japan) and bevacizumab (15 mg/kg) showed excellent activity against chemotherapy-naïve non-squamous NSCLC, with an ORR of 74.4 % (95 % CI, 60.0–88.7 %), a median PFS of 6.2 months (95 % CI, 4.8–8.5), and a median OS of 22.4 months (95 % CI, 11.3–26.2). The wide and deep tumor response, as demonstrated by a waterfall plot analysis, and the median OS of 22.4 months are even reminiscent of the outstanding results obtained using EGFR-TKIs for patients with EGFR-mutated NSCLC. The primary endpoint was met because the lowest end of the 95 % CI of the median PFS exceeded the predefined criteria of 4.6 months. Although manageable, toxicities of grade 3 or higher were relatively frequent, including hypertension in 38.5 % of the treated patients, neutropenia in 71.8 %, and febrile neutropenia in 23.1 %. Although the rate was comparable to those observed in previous studies, i.e., 53 % in the Eastern Cooperative Oncology Group (ECOG) study [12] and 41 % in the AVAiL study [13], only 54 % of the patients proceeded to the maintenance phase despite the higher ORR in this study. This might have been a consequence of the frequency of neutropenia and febrile neutropenia. In fact, the protocol treatment was discontinued because of toxicity in 44 % of the patients.

At least three meta-analyses demonstrated significantly improved ORR and PFS by adding bevacizumab to platinum-based two-drug chemotherapy for NSCLC [27–29]. With regard to OS, however, although two meta-analyses [28, 29] disclosed a small but statistically significant improvement in OS with the addition of bevacizumab, another meta-analysis [27] failed to show the advantage of adding bevacizumab. These advantages, however, are accompanied by the cost of a slightly increased incidence of toxicities, including bleeding, thromboembolism, proteinuria, hypertension, neutropenia, and febrile neutropenia. In addition, with a wide variety of cancers including NSCLC, a meta-analysis disclosed an increased risk of treatment-related mortality due to combining bevacizumab with chemotherapy or biological therapies [30]. The evaluated regimens in the randomized studies included in the meta-analyses for NSCLC, however, were limited to carboplatin plus paclitaxel and cisplatin plus gemcitabine. To expand the clinical utility of bevacizumab in front-line treatment of patients with non-squamous NSCLC, a variety of combinations have been reported with promising results. These combinations include regimens with oxaliplatin [31–33] as a platinum agent, vinorelbine [34], docetaxel [33, 35–37], pemetrexed [32, 38–41], nanoparticle albumin-bound paclitaxel [42], oral S-1 [43, 44], and ixabepilone [40]. The present study provided further evidence of the high efficacy of a 3-drug combination chemotherapy including bevacizumab for the treatment of advanced non-squamous NSCLC. Although the frequency of neutropenia (≥grade 3) and febrile neutropenia were somewhat high, all the complications were transient and easily manageable. The remaining toxicities were all mild and manageable.

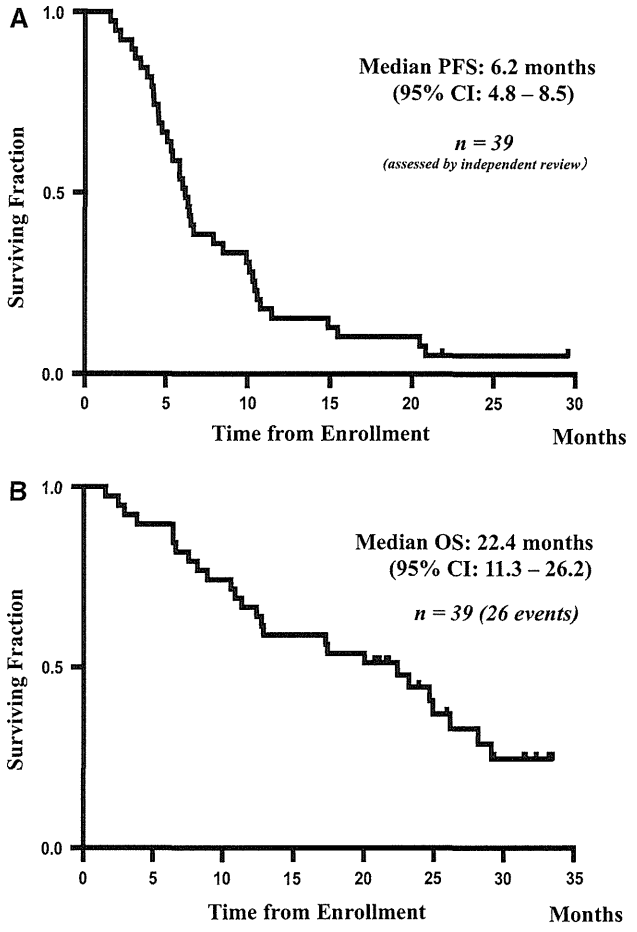

Fig. 2 Cumulative probability of progression-free survival (**a**) and overall survival (**b**), estimated using the Kaplan–Meier method in 39 patients with non-squamous NSCLC who were treated in the present study. After a median follow-up period of 20.2 months, the median PFS and OS were 6.2 months (95 % CI, 4.8–8.5 months) and 22.4 months (95 % CI, 11.3–26.2 months), respectively. For the PFS analysis, 2 patients had not experienced progression and were thus censored, while for the OS analysis, 13 patients had not experienced death and were censored. The *vertical lines* indicate the censored cases

William et al. [35] reported the results of a phase II study with the same combination except for a docetaxel dose of 75 mg/m^2 instead of 60 mg/m^2 in a study involving 40 patients with chemotherapy-naïve advanced non-squamous NSCLC. The results were also excellent, with an ORR of 53 %, median PFS as the primary endpoint of 7.9 months, and a median OS of 16.5 months. In this previous study, the hematological toxicity was milder than in the present study, with neutropenia (≥grade 3) and febrile neutropenia occurring in 33 and 10 % of the patients, respectively. On the other hand, they observed infectious events (≥grade 3) in 13 % of the patients and treatment-related deaths in 2 patients (5 %), whereas infectious events (≥grade 3) were observed in only 2.9 % of the patients in the present study and no treatment-related deaths occurred. Considering these results together, regimens containing carboplatin, docetaxel, and bevacizumab may require special caution with regard to the occurrence of neutropenia, febrile neutropenia, and infection as adverse events. As mentioned under "Statistical and ethical considerations" in the Introduction section, the aim of the study was to evaluate PFS of the new regimen with the addition of bevacizumab and the substitution of carboplatin in place of cisplatin, and we are considering performing a randomized study to compare the present regimen with combination chemotherapy consisting of cisplatin and docetaxel. In this case, reconsideration of the doses of carboplatin and docetaxel might be required.

In conclusion, combination chemotherapy consisting of carboplatin, docetaxel, and bevacizumab is promising as a front-line therapy for patients with advanced non-squamous NSCLC with excellent activities in terms of ORR, PFS, and OS. This regimen may be especially beneficial for patients with symptoms arising from a substantial volume of tumor burden because of its good ORR and the waterfall plot analysis findings. Further studies examining this regimen are warranted.

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Conflict of interest Yuichi Takiguchi received honoraria from AstraZeneca K.K., Chugai Pharmaceutical Co., Ltd., Sanofi K.K. and Ono Pharmaceutical Co., Ltd., and research funding from AstraZeneca K.K., Chugai Pharmaceutical Co., Ltd. and Sanofi K.K. Koichi Minato received honoraria from Chugai Pharmaceutical Co., Ltd., and research funding from Ono Pharmaceutical Co., Ltd. and Shionogi & Co., Ltd. Yosuke Miura received honoraria from Chugai Pharmaceutical Co., Ltd. Akihiko Gemma received honoraria from Chugai Pharmaceutical Co., Ltd., Novartis Pharma K.K., Bayer Yakuhin, Ltd., Pfizer Japan Inc. and Eli Lilly Japan K.K. Mitsunori Hino received honoraria from AstraZeneca K.K., Chugai Pharmaceutical Co., Ltd., Novartis Pharma K.K., GlaxoSmithKline K.K., Astellas Pharma Inc., and research funding from AstraZeneca K.K., Chugai Pharmaceutical Co., Ltd. and Astellas Pharma Inc. Hiroaki Okamoto received research fund from Chugai Pharmaceutical Co., Eli Lilly Japan K.K. and Sumitomo Dainippon Pharma Co., Ltd. Shunichiro Iwasawa, Rintaro Noro, Kozo Yoshimori, Masato Shingyoji and Masahiro Ando report no conflict of interest.

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Symptom Management and Supportive Care

A Prospective Study of Shortened Vitamin Supplementation Prior to Cisplatin–Pemetrexed Therapy for Non-Small Cell Lung Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Chemotherapy • Homocysteine • Non-small cell lung cancer • Pemetrexed • Vitamin supplementation

ABSTRACT

Background. Prior supplementation with folic acid and vitamin B_{12} is required to reduce pemetrexed therapy toxicity; the recommended lead-in time is at least 7 days. On the basis of previous pharmacokinetic and clinical studies, we hypothesized that the lead-in time could be shortened to 24 hours, enabling earlier commencement of standard chemotherapy; thus, we planned the first prospective trial of this regimen.

Methods. Patients with advanced nonsquamous non-small cell lung cancer who had not previously received cytotoxic chemotherapy were enrolled. After measurement of homocysteine concentrations, the patients received 1,000 μg of vitamin B_{12} by intramuscular injection and began taking 350–500 μg of oral folic acid daily. Starting 24–48 hours after the vitamin B_{12} injection, the patients received intravenous 500 mg/m^2 pemetrexed and 75 mg/m^2 cisplatin for 4 cycles at 3 weekly intervals. The primary endpoint was the proportion of patients who developed neutropenia grade ≥3.

Results. Thirty patients received chemotherapy starting within 48 hours of the vitamin B_{12} injection. No treatment-related deaths or grade 4 toxicity occurred. Neutropenia grade ≥3, other laboratory toxicities grade ≥3, and nonlaboratory toxicities grade ≥3 occurred in 6.7%, 13%, and 13% of patients, respectively. The baseline homocysteine concentrations were not higher in patients with grade ≥3 toxicities than in the remainder of the cohort (mean values, 8.6 and 10.7 μmol/L, respectively). The response rate to chemotherapy was 43%.

Conclusion. The shortened vitamin supplementation was well tolerated and retained antitumor efficacy. Analysis of baseline homocysteine concentrations confirmed the efficacy of short-term vitamin supplementation. ***The Oncologist*** 2014;19:1194–1199

Implications for Practice: Routine supplementation with folic acid and vitamin B_{12}, at least 1 week before the first pemetrexed administration, is necessary to reduce its toxicity, but the procedure can cause treatment delay. In daily practice, some patients experience disease progression before receiving planned treatment. Delayed start of pemetrexed-based chemotherapy can have a negative impact on patient outcomes because pemetrexed is an indispensable component of standard chemotherapy for non-small cell lung cancer. This study showed that the shortened vitamin supplementation before pemetrexed-based chemotherapy was well tolerated and retained antitumor efficacy, confirmed by the analysis of baseline total plasma homocysteine level.

INTRODUCTION

Pemetrexed (PEM) is an antifolate that inhibits multiple enzymes, including thymidylate synthase, glycinamide ribonucleotide transformylase, and dihydrofolate reductase [1]. In early studies of PEM, neutropenia, infection, and mucositis were frequently observed and sometimes life-threatening [2, 3]. To identify the predictive factors for PEM-related toxicities, a multivariate analysis incorporating a number of phase II trials was conducted [4]. This analysis showed that the pretreatment total plasma homocysteine (tHcy) concentration, a marker for folic acid and/or vitamin B_{12} deficiency, and methylmalonic acid concentration, a marker for vitamin B_{12} deficiency, can predict severe adverse events caused by PEM. On the basis of this finding, folic acid and vitamin B_{12} supplementation were added to the regimen in a phase III study of malignant mesothelioma treatment comparing cisplatin (CDDP) alone or CDDP + PEM during the accrual. This change resulted in a marked reduction of severe adverse events in the CDDP + PEM arm without diminishing antitumor efficacy [5].

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At present, the standard regimen consists of supplementation with 350–1,000 μg of oral folic acid daily during at least 1 week before the first dose of PEM [2]; however, there is no clear rationale for this particular lead-in time. Although the standard dose of folic acid intake preserves PEM activity [6], other preclinical studies indicated that excessive folic acid significantly diminishes the antitumor efficacy of PEM [7, 8]. In general, folic acid deficiency takes months to correct with folate intake, particularly when low doses of folic acid are administered [9]. Therefore, oral folic acid taken before initiating PEM therapy may have little effect: Toxicities caused by administering PEM without vitamin supplementation typically occur after 2 cycles of therapy [4].

In previous phase III studies, both folate and vitamin B_{12} have been administered 1 to 2 weeks before initiating PEM therapy [10]. However, a pharmacokinetic study using radioisotope-labeled vitamin B_{12} has shown that parenterally administered vitamin B_{12} begins to pervade the main organs within 1 hour of injection, achieving a plateau approximately 24 hours later [11]. Excessive vitamin B_{12} does not seem to affect the antitumor activity of antifolates: a 10-fold excess of vitamin B_{12} did not affect the activity of trimetrexate against colon cancer cell lines [7].

Therefore, we hypothesized that the lead-in time for vitamin supplementation could be shortened to 24 hours, thus enabling earlier commencement of standard chemotherapy and potential avoidance of treatment alterations because of rapid disease progression before the initiation of chemotherapy. To our knowledge, only a few retrospective analyses related to early initiation of PEM have been conducted [12]. Therefore, we initiated the first prospective study evaluating a shortened duration of vitamin B_{12} and folic acid supplementation before PEM-based chemotherapy.

Materials and Methods

The study described was a multicenter, open-label, single-arm phase II study. It was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Research issued by the Japanese Ministry of Health, Labor, and Welfare. The protocol was also approved by the institutional review board of each participating center. All patients gave their written informed consent. The clinical trial registry number is UMIN000006546.

Study Participants

Eligible patients were aged ≥20 years and had a stage IIIB/IV or recurrent nonsquamous non-small cell lung cancer. Patients had not received prior cytotoxic chemotherapy, but prior treatment by epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) was allowed. Additional inclusion criteria were Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, neutrophil count ≥1,500 cells per microliter, hemoglobin level ≥9.0 g/dL, platelet count ≥100,000 cells per microliter, aminotransferase ≤2.5× the upper limit of normal, total bilirubin ≤1.5× the upper limit of normal, creatinine clearance ≥45 mL/minute, oxygen saturation by pulse oximetry ≥92%, and life expectancy >12 weeks.

Patients were excluded if they had received surgery or radiotherapy within 3 weeks before enrollment or had a history of interstitial lung disease, active infectious disease, severe or uncontrollable comorbidities, symptomatic brain metastases, massive pleural effusion or ascites, or a malignancy that required treatment within 12 weeks after enrollment. Patients who needed to take folate or vitamin B_{12} continuously, or pregnant or nursing women also were excluded.

Treatment

After measurement of tHcy concentrations, patients were administered 1,000 μg of vitamin B_{12} by intramuscular injection. Then, they began to take once-daily oral multivitamins containing 350–500 μg of folic acid, which is the most common way of providing folate supplementation for PEM therapy in Japan. Within 24–48 hours of the vitamin B_{12} injection, 500 mg/m^2 PEM and 75 mg/m^2 CDDP were administered intravenously. Palonosetron, aprepitant, and dexamethasone were used to prevent chemotherapy-induced nausea and vomiting in accordance with the American Society of Clinical Oncology Clinical Practice Guidelines [13]. Treatment with CDDP + PEM was repeated every 3 weeks for 4 cycles unless there was evidence of disease progression or unacceptable toxicity. Vitamin B_{12} was injected again on day 21 of cycle 3. After termination of the study treatment, any subsequent therapy, including maintenance therapy with PEM, was allowed.

If a patient experienced neutrophil count <500 cells per microliter, platelet count <50,000 cells per microliter, or grade 3 nonhematologic toxicities other than mucositis, a 25% dose reduction of both CDDP and PEM was recommended. If grade 2 neurotoxicity was observed, a 50% dose reduction of CDDP was recommended, and a 50% dose reduction of PEM was recommended when grade 3 mucositis was observed. Actual dose reduction depended on the decision of the attending investigator, but if a patient experienced the conditions defined above in 2 different cycles, study treatment was terminated. Grade 4 nonhematologic toxicities, grade 3 neurotoxicities, pneumonitis grade ≥2, treatment delay >14 days, and other conditions unsuitable for continuing chemotherapy also were conditions considered for study treatment termination.

Assessments

Toxicities were evaluated according to the National Cancer Institute's Common Toxicity Criteria for Adverse Events, version 4.0. Complete blood counts and serum chemistries were obtained on day 1 of each cycle, days 8 and 15 of the first cycle, and day 8 or 15 of subsequent cycles.

Tumor response to chemotherapy was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. After baseline evaluation, tumor status was assessed every 6 weeks (2 cycles). Toxicities and responses were evaluated in all patients who started chemotherapy within 48 hours of receiving the vitamin B_{12} injection.

Statistical Methods

The primary endpoint of this study was the proportion of patients who developed neutropenia grade ≥3. The subset analysis of East Asian participants of the JMDB study [14] was used as a historical cohort, in which the proportion of patients with neutropenia grade ≥3 was 27.7%. To detect the difference between the expected 30% of patients with neutropenia grade ≥3 and the null hypothesis of 50% using a 2-stage design with 70% power and 5% α (2-sided), 30 patients were to be accrued.

The secondary endpoints were other toxicities and response rate to chemotherapy. Exploratory endpoints included progression-free survival (PFS), overall survival (OS), relative dose intensity (RDI), and tHcy concentrations before vitamin supplementation. The number of months that elapsed between the enrollment and the date of disease progression or death was defined as PFS. Patients who remained alive without disease progression at the end of follow-up and patients who started subsequent chemotherapy without disease progression were censored. The number of months between study enrollment and date of death was defined as OS. Patients alive at the end of follow-up were censored. Both PFS and OS were estimated using the Kaplan-Meier method. The ratio of the delivered dose per unit of time divided by the planned dose per unit of time was defined as RDI. The relationship between baseline tHcy levels and toxicities of chemotherapy was evaluated using Student's *t* test, comparing patients who experienced any toxicities grade ≥3 with the remaining patients. All tests were two-sided, and the significance level was set at .05. All data were analyzed using JMP version 9.0 software (SAS Institute, Inc., Cary, NC, http://www.sas.com).

Results

Patient Characteristics

From November 2011 to March 2013, 31 patients diagnosed with stage IIIB/IV or recurrent nonsquamous non-small cell lung cancer at two institutes were enrolled (Table 1). The median age was 66 (range, 34–74) years, and 10 patients (32%) were female (Table 1). Most patients had adenocarcinoma (87%) and stage IV disease (90%). Eight patients (26%) and 1 patient (3%) presented EGFR mutations and anaplastic lymphoma kinase translocation, respectively. Eastern Cooperative Oncology Group PS was 0 in 16 patients (52%) and 1 in 15 patients (48%). Three patients (10%) had received prior EGFR-TKI therapy, and all 3 of these patients had an EGFR activating mutation. The mean baseline tHcy level was 10.6 (range, 5.5–23.8) μmol/L (median, 9.2 μmol/L; SD, 4.5 μmol/L).

Table 1. Patient characteristics

Category	Subcategory	*n* (%)
Total		31
Median age (range), yr		66 (34–74)
Sex	Female	10 (32%)
	Male	21 (68%)
Histologic type	Adenocarcinoma	27 (87%)
	NSCLC, NOS	4 (13%)
Disease stage	IIIB	2 (6%)
	IV	28 (90%)
	Recurrent	1 (3%)
PS	0	16 (52%)
	1	15 (48%)
Genetic profile	*EGFR* mutation	8 (26%)
	ALK translocation	1 (3%)
	Wild type	21 (68%)
	Unknown	1 (3%)
Average tHcy level (range), μmol/L		10.2 (5.5–23.8)

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; PS, performance status; tHcy, total plasma homocysteine.

Treatment

Thirty patients received CDDP + PEM within 24 to 48 hours after vitamin B_{12} injection. One patient could not start chemotherapy for 2 weeks after vitamin B_{12} injection because of hepatic toxicity caused by acetaminophen and was excluded from the following analyses. The median number of cycles delivered was 4, with 21 patients (70%) completing the 4 cycles of the study treatment (Fig. 1). Reasons for discontinuation were disease progression in six patients (20%) and adverse events in three patients (10%). Of 21 patients who completed 4 cycles of chemotherapy, 19 (90%) proceeded to maintenance therapy with PEM, with a median number of maintenance chemotherapy cycles of 6 (range, 1–17+). One patient (3%) required dose reduction because of renal toxicity caused by CDDP, and nine patients (30%) required delays in treatment for more than 3 days. The most common reasons for treatment delay were administrative (e.g., public holidays) or to suit patients' schedules; however, 3 patients (10%) had treatment delays because of adverse events. The RDIs for CDDP and PEM were 96.3% and 96.4%, respectively. When the influence of administrative delay was excluded, RDIs for CDDP and PEM were 98.7% and 98.7%, respectively.

Safety

No treatment-related deaths or grade 4 toxicity occurred (Table 2). The proportion of patients experiencing neutropenia grade ≥3 was 6.7% (95% confidence interval [CI], 0.8%–22.1%). Hematologic and nonhematologic toxicities grade ≥3 occurred in 13% and 13% of patients, respectively. The mean baseline tHcy concentration of the 8 patients who experienced any toxicities grade ≥3 was 8.6 (range, 6.7–12.2; median, 8.3; SD, 1.9) μmol/L, whereas the mean tHcy concentration of the remaining 22 patients was 10.7 (range, 5.5–23.8; median 10.2; SD, 4.5) μmol/L. The differences between patients who did and did not experience serious toxicities are not statistically significant (Fig. 2).

Antitumor Efficacy

All the enrolled patients had measurable lesions defined by RECIST. The response rate to chemotherapy was 43% (95% CI, 27%–61%), and the disease control rate was 77% (95% CI, 59%–88%). At a median follow-up time of 18.4 months, the median PFS and OS were 5.7 months (95% CI, 4.1–10.7 months) and 22.9 months (95% CI, 13.4–26.2 months), respectively (Fig. 3).

Discussion

In this first prospective study to evaluate shortened vitamin B_{12} and folate supplementation for PEM-based chemotherapy, toxicities caused by CDDP + PEM were not greater than in the historical cohort, and the antitumor efficacy of the therapy was retained. Baseline tHcy, known as a predictive marker of