However, platinum-doublet chemotherapy has been recommended for patients with NSCLC with a performance status (PS) of 0 or 1,[6-8] and several retrospective subgroup analyses of large phase III trials have shown that the efficacy of platinum-doublet chemotherapy is similar in selected elderly patients and younger patients.[9,10] However, drug excretion or metabolic abilities generally decline because of age-related insufficiencies, especially in renal function. Therefore, modifications of anticancer drug dosages or schedules are recommended in chemotherapy for elderly patients with cancer.[11] In Japan, phase I[12] and II trials of weekly docetaxel plus cisplatin (DP) were conducted in elderly patients with NSCLC. The phase II study revealed a response rate (RR) of 52% (95% CI, 31% to 67%), a median survival time of 15.8 months, and no grade 4 toxicity.[13] On the basis of these promising results, we conducted a randomized phase III trial, the Japan Clinical Oncology Group (JCOG) 0207 trial, to compare DP with single-agent docetaxel. For the control arm, we chose weekly split docetaxel to investigate the effects of added cisplatin. In the second interim analysis, the overall survival (OS) seemed to be more favorable in the DP arm; however, an unexpected large difference was observed in the subgroup of patients age less than 75 years.[14] Therefore, considering the potential disadvantage of single-agent docetaxel therapy in this subgroup, we terminated the study and designed a new phase III trial in which the control arm received bolus infusions of docetaxel every 3 weeks, based on the West Japan Thoracic Oncology Group 9904 study.[5]

PATIENTS AND METHODS

Patients

Patients eligible for this study included chemotherapy-naïve patients with histologically or cytologically confirmed stage III (no indication for definitive radiotherapy), stage IV, or recurrent NSCLC who were age ≥ 70 years, with an Eastern Cooperative Oncology Group PS of 0 or 1 and adequate organ functioning, but who were unsuitable for bolus cisplatin administration. Considering that the age group of 70 to 74 years included those who were suitable and unsuitable for bolus cisplatin administration, we classified the reasons for administration unsuitability in this age group into six categories and examined patients for these conditions before enrollment. The pre-enrollment evaluation is described in the Appendix and Appendix Table A1 (online only). Prior radiotherapy, except for the primary lesion, was permitted if it had been completed at least 2 weeks before enrollment onto the study. Patients with symptomatic brain metastasis, active malignancy within the previous 5 years, superior vena cava syndrome, massive pleural effusion or ascites, critical vertebral metastasis, uncontrolled hypertension or diabetes, severe heart disease, active infection, hepatitis virus B surface antigen seropositivity, pulmonary fibrosis, polysorbate 80 hypersensitivity, or steroid dependence were excluded.

The study protocol was reviewed and approved by the JCOG Protocol Review Committee, WJOG executive board, and institutional review boards of each participating institution before study initiation. All patients provided written informed consent before enrollment.

Study Design and Treatment Plan

Eligible patients were randomly assigned to either the docetaxel arm (docetaxel 60 mg/m^2 infused over 60 minutes on day 1 every 3 weeks) or the DP arm (docetaxel 20 mg/m^2 infused over 60 minutes plus cisplatin 25 mg/m^2 infused over 15 to 20 minutes on days 1, 8, and 15 every 4 weeks). Patients were randomly assigned via the minimization method to balance the arms with the institution, disease stage (III *v* IV or recurrence), and age ($\geq v < 75$ years). In the DP arm, treatment was skipped under the following conditions: total leukocyte count less than 2,000/μL, platelet count less than 50,000/μL, creatinine level ≥ 1.5 mg/dL, and presence of fever or grade ≥ 3 nonhematologic toxicity (except constipation, weight loss, cough, hoarseness, and hyponatremia) on day 8 or 15. In both arms, subsequent cycle treatment was administered when the patients met the following conditions: total leukocyte count ≥ 3,000/μL, absolute neutrophil count ≥ 1,500/μL, platelet count ≥ 100,000/μL, serum creatinine level less than 1.5 mg/dL, total bilirubin level less than 2.0 mg/dL, ALT/AST ≤ 100 IU/L, and PS 0 to 2. Administration procedures, dose reduction criteria, and methods are detailed in the Appendix. Both treatments were repeated until the detection of disease progression or appearance of unacceptable toxicity. Radiographic tumor evaluations were performed and assessed, according to RECIST (version 1.0),[15] by each investigator at least every two cycles. Laboratory examinations were performed at least once a week in both arms, and toxicity was assessed before every cycle and classified in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Second-line treatment was administered at the investigator's discretion; however, cross-over to the other treatment arm was not permitted.

Quality-of-Life Assessment

Quality of life (QOL) was assessed by symptom scores, using the seven items of the Lung Cancer subscale of the Functional Assessment of Cancer Therapy–Lung.[16] The patients scored themselves immediately after providing informed consent and after completing the second and third treatment cycles. The proportions of patients with improved scores between the baseline and the end of the third cycle in each arm were compared. Missing data after treatment initiation were considered as indicating no improvement. In addition, we compared least squared means of the total scores from repeated measures analysis of variance with treatment arm, time, and their interaction and the 95% CI at each time point.

Supplementary Ad Hoc Analysis

Additional data collection and ad hoc analysis were performed. Data on the active epidermal growth factor receptor (*EGFR*) mutation status (exon 19 deletion or L858R point mutation) and poststudy treatments were collected because these were considered factors that could potentially affect survival.

Statistical Analysis

OS was the primary trial end point. The secondary end points included RRs, progression-free survival (PFS), symptom scores, and toxicities. The study was designed to provide results with a statistical power of 80%, using a one-sided $\alpha = .05$ to detect a 33% increase in median survival from 10 to 13.3 months. A total of 364 patients was required, accrued over a 4-year period with a 1-year follow-up period. Assuming a 5% rate of ineligible patients and patients lost to follow-up, the study sample size was set at 380 patients. OS, PFS, and responses were assessed in all eligible patients on an intent-to-treat basis. OS and PFS, which are defined in the Appendix, were estimated using the Kaplan-Meier method and were compared using the stratified log-rank test, according to age. Hazard ratios (HRs) of the treatment effects were estimated using the Cox proportional hazards model. RRs were compared using Fisher's exact test.

Two interim analyses were planned, the first after 50% of the patients were enrolled and the second after enrollment was completed. In these interim analyses, the primary end point, OS, was evaluated after adjustment for multiple comparisons, according to the Lan and DeMets method.[17] The O'Brien-Fleming–type α spending function was used. *P* values presented for the primary analysis were one-sided, in accordance with the trial design, whereas the other analysis values were two-sided. All analyses were performed using SAS software, release 9.1 (SAS Institute, Cary, NC). This study is registered with University Hospital Medical Information Network Clinical Trials Registry (www.umin.ac.jp/ctr/; identification No.: UMIN000001424).

RESULTS

The first interim analysis was performed in September 2010 and included data from 221 patients. Information time, defined as the

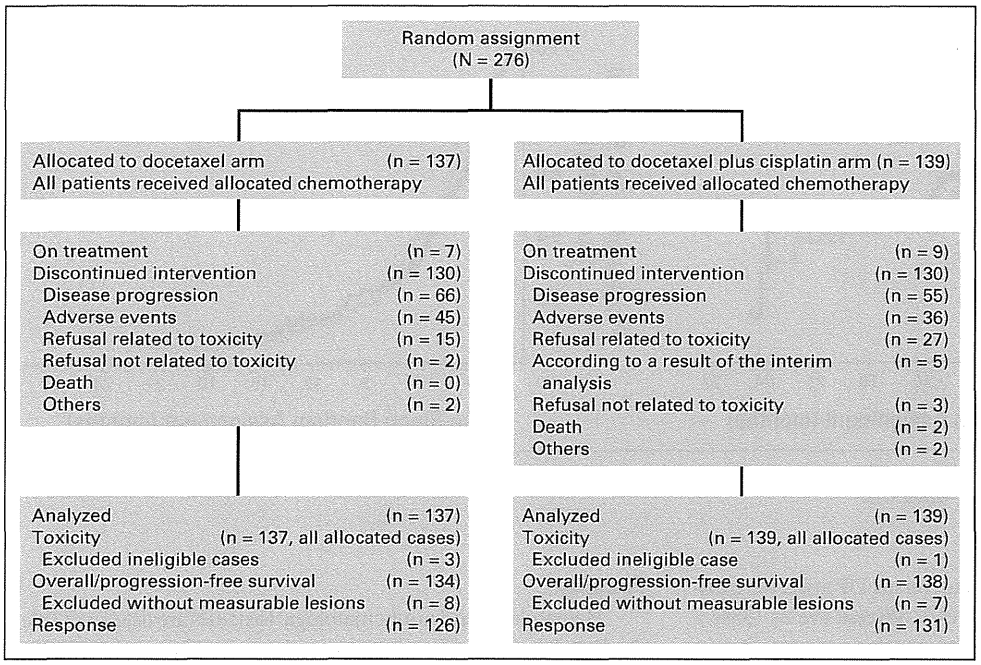

Fig 1. CONSORT diagram.

proportion of the interim events to the planned events, was 0.24 (73 of 304 events). Survival in the DP arm was inferior to that in the docetaxel arm (HR for DP to docetaxel arm, 1.56; 95% CI, 0.98 to 2.49; multiplicity-adjusted 99.99% CI, 0.62 to 3.88; one-sided $P = .97$ and two-sided $P = .06$ by stratified log-rank test), and the predictive probability that DP would be statistically superior to docetaxel on final analysis was 0.996% (< 1%). These results led to early study termination based on the recommendation of the Data and Safety Monitoring Committee, in accordance with the stopping guidelines prespecified in the protocol.

Patient Characteristics

Between October 2008 and September 2010, 276 patients (215 patients from JCOG and 61 patients from WJOG) were enrolled from 56 institutions (36 institutions affiliated with JCOG and 20 institutions affiliated with WJOG). Of these patients, 137 and 139 patients were assigned to the docetaxel and DP arms, respectively. All patients received the study treatments; therefore, all 276 patients were included in the safety analysis set. Three patients in the docetaxel arm and one patient in the DP arm were ineligible because of uncontrolled diabetes (ie, dependence on insulin injections) or previous malignancy. Therefore, these patients were excluded from survival analyses (Fig 1). Although the proportions of female patients and patients with adenocarcinoma were slightly higher in the docetaxel arm than in the DP arm, the patients' baseline characteristics were generally well balanced between the treatment arms (Table 1).

Treatment Delivery

The median number of treatment cycles was four (range, one to 18 cycles) in the docetaxel arm and three (range, one to six cycles) in the DP arm, and the proportion of patients in whom treatment continued for five or more cycles was higher in the docetaxel arm than in the DP arm (31% *v* 8%, respectively). In the docetaxel and DP arms, 37% and 4% of patients required one-step dose reductions, respectively. Furthermore, 19% of patients required two-step dose reductions in the docetaxel arm. In the DP arm, 19% of patients had one or more skipped treatments on day 8 or 15. The major reasons for

Table 1. Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	Docetaxel (n = 137)		Docetaxel/Cisplatin (n = 139)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	76		76	
Range	70-87		70-86	
< 75	31	23	32	23
≥ 75	106	77	107	77
Sex				
Male	95	69	101	73
Female	42	31	38	27
Smoking status*				
Never	38	28	36	26
Smoker	98	72	101	74
ECOG PS				
0	50	36	48	35
1	87	64	91	65
Stage				
III	42	31	43	31
IV or recurrence	95	69	96	69
Histology*				
Adenocarcinoma	91	67	86	63
Squamous	32	24	39	28
Others	13	10	12	9

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.
*Data for one patient in the docetaxel monotherapy arm and two patients in the docetaxel plus cisplatin arm were missing.

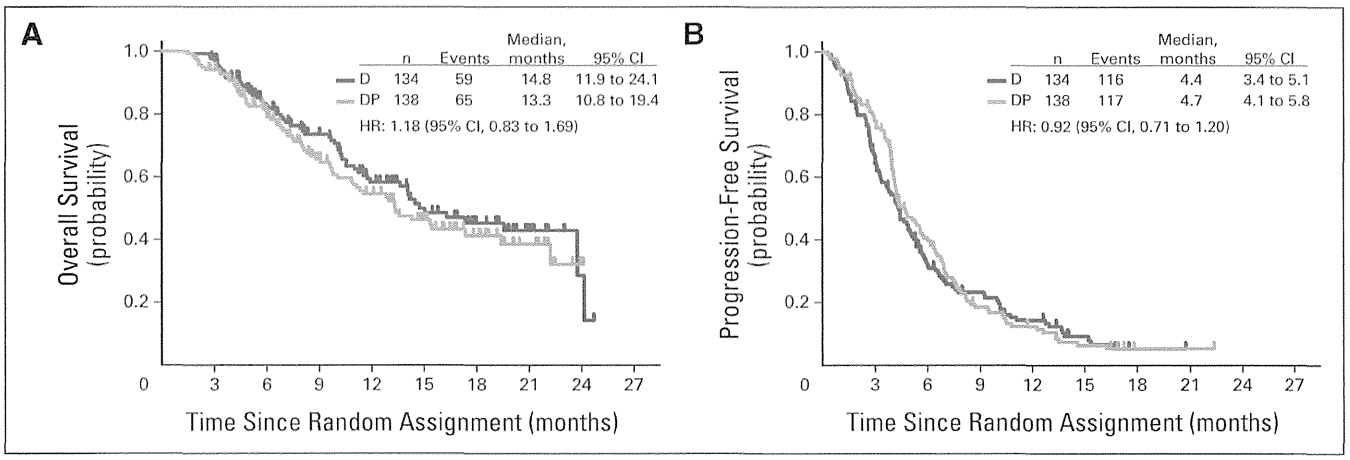

Fig 2. Kaplan-Meier curves for (A) overall survival and (B) progression-free survival. Tick marks indicate censored patients at the data cutoff point (November 2010). D, docetaxel; DP, docetaxel plus cisplatin; HR, hazard ratio.

treatment discontinuation in the docetaxel versus DP arms were disease progression (51% *v* 42%, respectively), adverse events (35% *v* 28%, respectively), and patient refusal to continue treatment as a result of toxicity (12% *v* 21%, respectively).

Efficacy

The overall RRs were 24.6% in the docetaxel arm (95% CI, 17.4% to 33.1%) and 34.4% in the DP arm (95% CI, 26.3% to 43.2%). The difference was not statistically significant ($P = .10$).

By November 22, 2010, 124 (45.6%) of the 272 eligible patients had died (docetaxel arm, n = 59; DP arm, n = 65). The median follow-up time for all eligible patients was 9.6 months. The 1-year survival rates were 58.2% and 54.5% in the docetaxel and DP arms, respectively. The HR for OS was 1.18 (95% CI, 0.83 to 1.69; Fig 2A). The HR for PFS was 0.92 (95% CI, 0.71 to 1.20; Fig 2B).

Toxicity

Hematologic and nonhematologic toxicities are listed in Table 2. Grade ≥ 3 leukopenia and neutropenia occurred more frequently in the docetaxel arm. The incidence of grade 4 neutropenia was 67.9% in the docetaxel arm but only 0.8% in the DP arm. Febrile neutropenia was observed only in the docetaxel arm at an incidence of 15.2%. Grade ≥ 3 anemia, hyponatremia, and anorexia were observed in more than 10% of patients in the DP arm. Four treatment-related deaths occurred, all in the DP arm (2.9%), including three patients who died of pneumonitis and one patient who died of unclassified sudden death.

QOL

Symptom score questionnaire responses were collected from 271 (98.2%) of 276 patients at baseline, 258 patients (93.5%) after the second cycle, and 247 patients (89.5%) after the third cycle. The

Table 2. Toxicities

	Docetaxel (n = 137)			Docetaxel/Cisplatin (n = 139)		
Adverse Event	Grade 3 or 4 (%)	Grade 4 (%)	Missing (No.)	Grade 3 or 4 (%)	Grade 4 (%)	Missing (No.)
Hematologic*						
Leukopenia	62.7	8.2	3	5.4	0	10
Neutropenia	88.8	67.9	3	10.1	0.8	10
Anemia	3.7	0.7	3	16.3	0.8	10
Thrombocytopenia	0	0	3	0.8	0	10
Nonhematologic*						
Febrile neutropenia	15.2	0	5	0	0	8
Hyponatremia	5.2	0.7	3	14.7	0.8	10
Hypoalbuminemia	1.5	—	6	4.7	—	10
Infection	7.6	0	5	8.4	0.8	8
Anorexia	1.5	0	5	10.7	0	8
Nausea	0.8	0	5	3.8	0	8
Diarrhea	3.8	0	5	0.8	0	9
Fatigue	3.0	0	5	5.3	0	8
Pneumonitis	5.3	0	5	2.3	0.8	8

NOTE. There were four treatment-related deaths (2.9%), all in the docetaxel plus cisplatin arm, including three deaths resulting from pneumonitis and one unclassified sudden death.
*Each value was calculated while excluding patients with missing data.

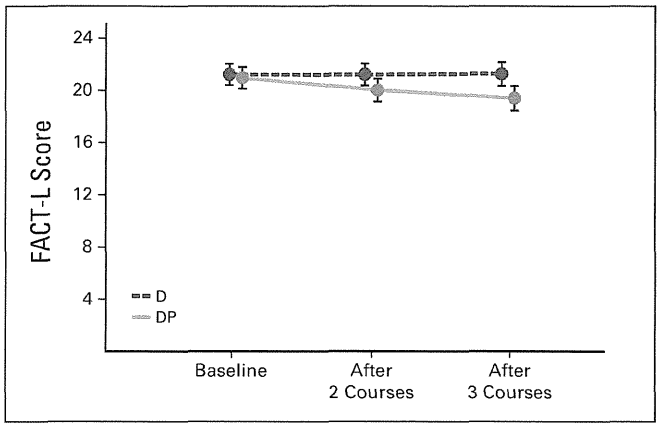

Fig 3. Quality-of-life assessments according to the seven-item Functional Assessment of Cancer Therapy–Lung (FACT-L). Dots and error bars indicate the least squared mean total scores and 95% CI, respectively. Higher scores indicate a better quality of life. D, docetaxel; DP, docetaxel plus cisplatin.

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.

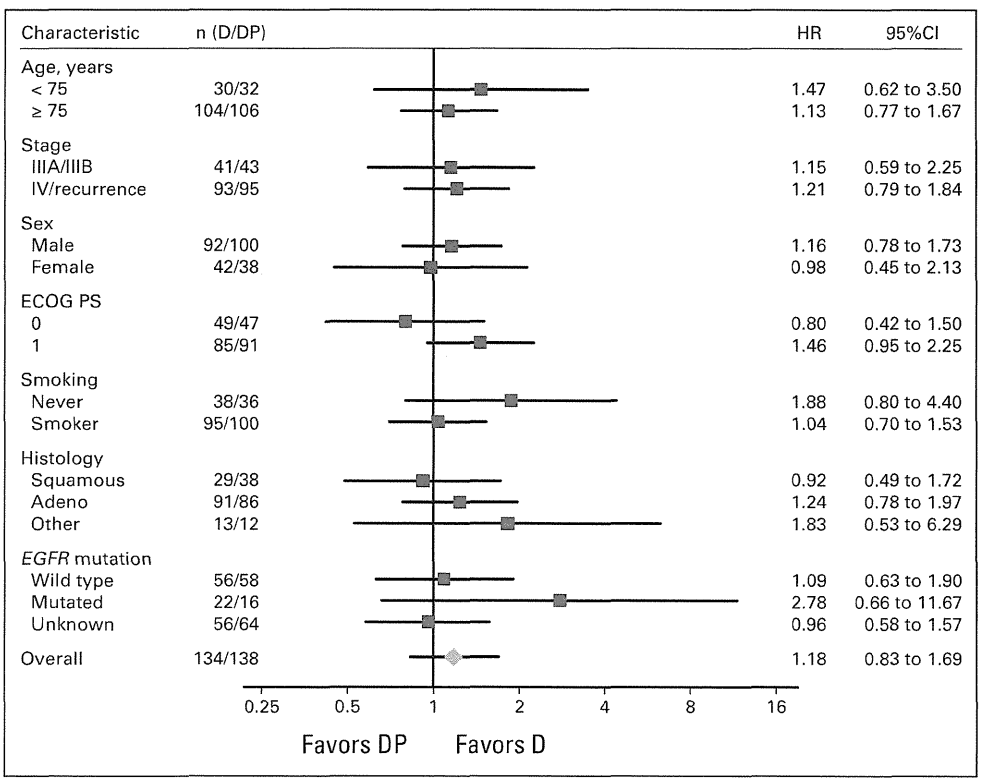

Fig 4. Subgroup analysis of overall survival. D, docetaxel; DP, docetaxel plus cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

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 ≥ 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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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

Gastric Cancer
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ORIGINAL ARTICLE

Randomized phase II trial of nimotuzumab plus irinotecan versus irinotecan alone as second-line therapy for patients with advanced gastric cancer

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Abstract

Background This multicenter, randomized phase II trial was conducted to compare the efficacy and safety of nimotuzumab plus irinotecan (N-IRI) versus irinotecan alone (IRI) in patients with advanced gastric cancer (AGC) showing disease progression after previous 5-fluorouracil-based therapy.

Methods Irinotecan-naive patients ($n = 82$) received N-IRI (nimotuzumab 400 mg weekly plus irinotecan 150 mg/m^2 biweekly) or IRI (irinotecan 150 mg/m^2 biweekly) until disease progression. The primary endpoint was progression-free survival (PFS), and the secondary endpoints were overall survival (OS), response rate (RR), safety, tolerability, and the correlation between efficacy and tumor epidermal growth factor receptor (EGFR) expression.

Results Of 83 patients, 40 and 43 patients were randomly assigned to the N-IRI and IRI groups, respectively. In the N-IRI/IRI treatment group, median PFS was 73.0/85.0 days ($P = 0.5668$), and median OS and RR at 18 months were 250.5/232.0 days ($P = 0.9778$) and 18.4/10.3 %, respectively. Median PFS and OS in the EGFR 2+/3+ subgroups were 118.5/59.0 and 358.5/229.5 days, respectively. The RR was 33.3/0.0 % in the N-IRI/IRI treatment group. The incidence of grade 3 or higher adverse events was 77.5/64.3 %. No adverse events of

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grade 3 or higher skin rash or grade 3 or higher infusion-related reaction were reported.
Conclusions There was no superiority of N-IRI over IRI alone in terms of PFS in 5-fluorouracil-refractory AGC patients. However, N-IRI showed potential improvement in the EGFR 2+/3+ subgroup based on improved RR, PFS, and OS.

Keywords Nimotuzumab · Anti-EGFR · Irinotecan · Second-line therapy · Advanced gastric cancer

Introduction

Patients with unresectable gastric cancer receiving the best supportive care have poor outcomes, with median survival times ranging from 3 to 5 months [1, 2]. In the metastatic disease setting, palliative chemotherapy improves survival compared with supportive care alone, with combined drug therapy yielding the best results [1–3]. Although there is no universally accepted standard treatment for advanced gastric cancer (AGC), several combination regimens have been used as first-line treatment, including epirubicin–oxaliplatin–capecitabine [4], cisplatin–capecitabine [5], cisplatin-S-1 [6], cisplatin–5-fluorouracil, and docetaxel–cisplatin–5-fluorouracil [7]. However, the median survival has not exceeded 8–13 months [1–7], and second-line treatments need to be established. Irinotecan [8, 9] or paclitaxel monotherapy is commonly used for AGC patients as second-line treatment, especially in Japan and Korea. Because of the limitations of the current therapies, addition of molecular-targeted drugs, particularly to chemotherapies with acceptable toxicities, may improve the outcomes. The ToGA trial demonstrated that the addition of trastuzumab to standard chemotherapy in patients with human EGFR-2 (HER-2)-overexpressing tumors improved overall survival (OS) and progression-free survival (PFS) [10].

Epidermal growth factor receptor (EGFR) is known to be expressed in a variety of tumors [11]. Approximately 30 % of gastric cancers are reported to show EGFR overexpression [12, 13]. EGFR signaling pathways are frequently dysregulated in gastric cancer, thereby serving as attractive therapeutic targets.

Nimotuzumab, a recombinant humanized monoclonal immunoglobulin G_1 antibody against human EGFR (HER-1), blocks the binding of epidermal growth factor (EGF) and transforming growth factor-α to EGFR. This mechanism regulates antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, inhibiting tumor cell growth and angiogenesis and inducing apoptosis [14–17]. In a previous phase I study in Japan, the safety and tolerability of nimotuzumab were investigated up to 400 mg doses weekly [18]. When combined with radiotherapy or chemoradiotherapy, nimotuzumab exerts clinical efficacy against head and neck cancers, gliomas, and non-small cell lung cancer (NSCLC) [17, 19, 20]. Additionally, because of the low frequency of severe dermatological toxicity, nimotuzumab is expected to improve the quality of life.

The present study was an open-label, phase II collaborative study between Japan and Korea. The primary objective was to compare PFS following combined nimotuzumab plus irinotecan therapy (N-IRI) and irinotecan monotherapy (IRI) in patients with unresectable or recurrent gastric cancer refractory to 5-fluorouracil-based therapy.

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Materials and methods

Patients

Patients in Japan and Korea were enrolled in this multicenter, open-label, randomized phase II trial. Patients with histologically confirmed AGC refractory to previous 5-fluorouracil-based chemotherapy for metastatic disease were eligible. Other major inclusion criteria were as follows: age of 20–75 years; adequate organ function; and Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1. Major exclusion criteria were prior exposure to irinotecan or EGFR-directed therapy, and significant comorbidities, such as diarrhea, interstitial pneumonia, or pulmonary fibrosis.

The trial was conducted in accordance with the Declaration of Helsinki. All the patients provided written informed consent. The institutional review boards or ethics committees of all participating centers reviewed and approved the protocol.

Study treatment

Patients were randomly assigned at a ratio of 1:1 to the N-IRI or IRI group by a computer program on the basis of the resection status of the primary tumor (inoperable advanced/postoperative recurrent) and study site, using the random permuted blocks method. Neither the patients nor the investigators were blinded to the treatment assignment.

Nimotuzumab (400 mg) diluted in normal saline to a total volume of 250 ml was administered once weekly by intravenous infusion over 30 min. Irinotecan (150 mg/m^2) was administered every 2 weeks. Treatment was continued until disease progression, appearance of unacceptable toxicity, or withdrawal of consent.

Efficacy and safety assessments

The primary endpoint was PFS following N-IRI versus IRI treatment. PFS was defined as the time from randomization to the day of documentation of progression or death, whichever was earlier. The secondary endpoints were OS, response rate (RR), disease control rate (DCR), safety, and tolerability. Tumor assessment by computed tomography was performed at baseline, and then every 4 weeks for the first 16 weeks, and every 6 weeks thereafter. Evaluation of tumors was performed by an independent Efficacy Evaluation Committee using RECIST 1.0. Adverse events were assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0.

Exploratory biomarker analysis

EGFR protein expression levels, *EGFR* gene amplification status, *K-ras* mutations, and HER-2 protein expression levels were measured in tissue specimens from tumors obtained from patients who had provided informed consent for exploratory biomarker analysis. The tumor tissues were centrally tested and classified. EGFR expression was analyzed using an immunohistochemistry (IHC) staining kit (EGFR PharmDX; Dako, Copenhagen, Denmark) and classified into four categories (0, 1+, 2+, and 3+), as previously described [21]. The *EGFR* gene copy number was measured by fluorescence in situ hybridization (FISH), as reported previously [22]. For *K-ras* mutation analysis, DNA was extracted from formalin-fixed paraffin-embedded tumor samples. The sequences of *K-ras* codons 12 and 13 and the surrounding region of the gene were analyzed by conventional polymerase chain reaction followed by direct sequencing. The expression status of HER-2 was analyzed using the HercepTest kit (Dako) and classified into four categories (0, 1+, 2+, and 3+).

Statistical analysis

The reported median PFS in AGC patients treated with irinotecan or paclitaxel as second-line chemotherapy is 2.1–2.6 months [23–25]. For an exploratory study, if the median PFS times for N-IRI and IRI therapy are assumed to be 4.5 and 2.5 months, respectively, then 32 patients per treatment arm would be required to detect a difference with 80 % power at a 10 % significance level using a one-sided log-rank test of the equality of survival curves. Assuming a dropout rate of 20 %, the number of patients per treatment group was set at 40, with a total sample size of at least 80 patients. The median PFS was calculated with the 95 % confidence interval (CI) for both treatment groups. Log-rank tests were performed to evaluate differences in PFS with the significance level set at 10 % (one sided). Primary statistical analysis of the efficacy endpoint was performed 6 months after registration of the last patient for the study.

For subgroup analyses of PFS and OS, the hazard ratio (HR) and 95 % CI within each subgroup were displayed in forest plots. In both treatment groups, the Kaplan–Meier method was used to plot the survival curves and estimate the cumulative incidence from the day of registration to death, as well as the cumulative incidence to disease progression. For evaluation of efficacy, point estimates were calculated for the RR and DCR and compared using the chi-squared test. Efficacy endpoints were analyzed using the full analysis set, safety endpoints were analyzed using the safety analysis set, and pharmacokinetic analyses were performed using the pharmacokinetic analysis set.

Results

Patients

A total of 83 patients were randomized from September 2008 to December 2009. Of these patients, 82 were included in the safety and efficacy analysis population (1 patient from the IRI group did not have a target lesion and did not receive irinotecan; Fig. 1). At the 18-month follow-up after registration of the last patient for the study, the median nimotuzumab and irinotecan exposure in the N-IRI group was 71.5 days (range, 8–947) and 60.5 days (range, 1–268), respectively, and the median irinotecan exposure in the IRI group was 57.0 days (range, 1–953). The median follow-up period was 242.5 days (range, 22–955). Patient demographics, including the UGT1A1 subtype, were well matched between the two treatment groups (Table 1).

Of the 83 patients, 48 patients had provided informed consent for exploratory biomarker analysis and submitted tumor samples. The EGFR protein expression level was detected in the assessable tumor tissues of 47 patients (57.3 % of the full analysis set population) (Table 2).

Efficacy

A total of 77 patients ($n = 38$ in the N-IRI group and $n = 39$ in the IRI group) were evaluable for radiologic tumor responses by an Independent Efficacy Evaluation Committee. PFS evaluated at 6 months after registration of the last patient was not significantly different between the treatment groups [median (95 % CI), 73.0 (55.0–112.0) days in the N-IRI group vs. 85.0 (37.0–93.0) days in the IRI group; HR (95 % CI), 0.860 (0.516–1.435), $P = 0.5668$] (Fig. 2).

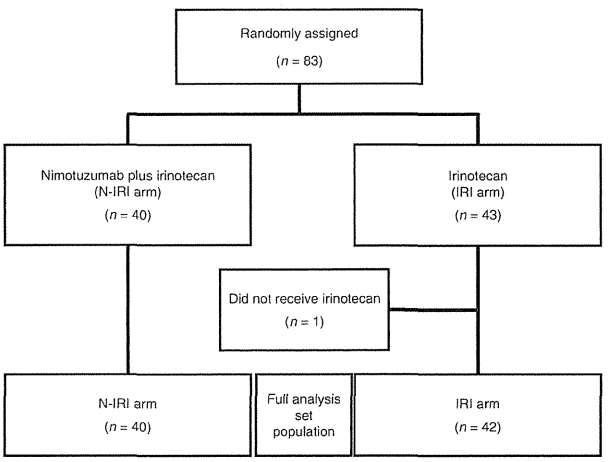

Fig. 1 CONSORT diagram. *N-IRI* nimotuzumab plus irinotecan, *IRI* irinotecan alone

By 18 months after registration of the last patient, 34 patients from each group had died and the 18-month OS was not significantly different between the treatment groups [median (95 % CI), 250.5 (171.0–306.0) days in the N-IRI group vs. 232.0 (148.0–319.0) days in the IRI group; HR (95 % CI), 0.994 (0.618–1.599), $P = 0.9778$]. There

Table 1 Baseline characteristics of the patients

Characteristics	N-IRI arm ($n = 40$)		IRI arm ($n = 42$)		Total ($n = 82$)	
	n	%	*n*	%	*n*	%
Age (years)						
Median	60.0		63.5		61.5	
Range	27–75		32–75		27–75	
Sex						
Male	33	82.5	33	78.6	66	80.5
Female	7	17.5	9	21.4	16	19.5
ECOG performance status						
0	19	47.5	17	40.5	36	43.9
1	21	52.5	25	59.5	46	56.1
Body weight (kg)						
Median	56.3		54.2		56.0	
Range	42.0–81.4		37.5–107.0		37.5–107.0	
Resection status of the primary tumor						
Inoperable advanced	22	55.0	23	54.8	45	54.9
Postoperative recurrent	18	45.0	19	45.2	37	45.1
Histological diagnosis, *n*						
Well/moderately differentiated adenocarcinoma	15	37.5	19	45.2	34	41.5
Poorly differentiated adenocarcinoma	21	52.5	17	40.5	38	46.3
Others	4	10.0	6	14.3	10	12.2
Primary tumor site						
Absent	18	45.0	16	38.1	34	41.5
Present	22	55.0	26	61.9	48	58.5
Gastroesophageal junction	4	18.2	1	3.8	5	10.4
Gastric region	18	81.8	25	96.2	43	89.6
Metastatic focus site						
No	1	2.5	0	0.0	1	1.2
Yes	39	97.5	42	100.0	81	98.8
Lymph node	25	64.1	25	59.5	50	61.7
Liver	13	33.3	19	45.2	32	39.5
Lung	3	7.7	6	14.3	9	11.1
Other	19	48.7	18	42.9	37	45.7
UGT1A1 gene polymorphism						
*1/*1, *1/*6, *1/*28	38	95.0	39	92.9	77	93.9
*6/*6, *28/*28, *6/*28	2	5.0	3	7.1	5	6.1

N-IRI nimotuzumab plus irinotecan, *IRI* irinotecan alone, *n* number of patients, *ECOG* Eastern Cooperative Oncology Group

Table 2 EGFR and HER-2 protein expression levels identified by immunohistochemistry

	EGFR							
	0		1+		2+, 3+		Total	
	n	%	*n*	%	*n*	%	*n*	%
HER2								
0	15	31.3	8	16.7	8	16.7	31	64.6
1+	2	4.2	2	4.2	5	10.4	9	18.8
2+, 3+	4	8.3	2	4.2	1	2.1	7	14.6
Total	21	43.8	12	25.0	14	29.2	47[a]	97.9

EGFR epidermal growth factor receptor, *n* number of patients, *HER2* human EGFR-2

[a] One sample was "not detected"

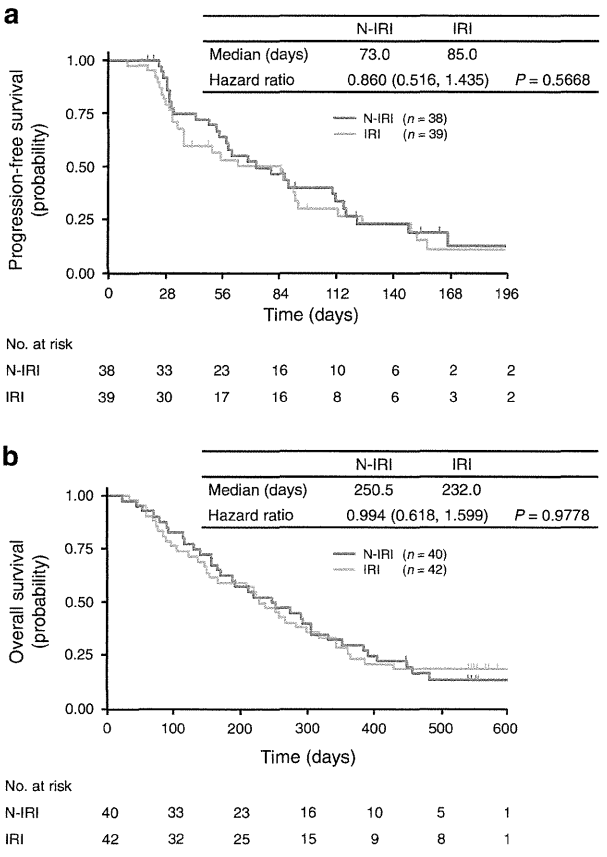

Fig. 2 Kaplan–Meier estimates of progression-free survival (**a**) and overall survival (**b**). *N-IRI* nimotuzumab plus irinotecan, *IRI* irinotecan alone

was no significant difference in RR or DCR at the 18-month follow-up between the treatment groups (RR, 18.4 % in the N-IRI group vs. 10.3 % in the IRI group, $P = 0.3060$; DCR, 47.4 % in the N-IRI group vs. 46.2 % in the IRI group, $P = 0.9150$).

PFS and OS in the various subgroups analyzed were not significantly different between the treatment groups (Fig. 3). However, the HR (IRI/N-IRI) in the EGFR 2+/3+ subgroup was lower than that in the entire treatment group. First, the median PFS (95 % CI) was 118.5 (87.0–not estimated) days for six patients in the N-IRI group vs. 59.0 (24.0–113.0) days for six patients in the IRI group [HR (95 % CI), 0.341 (0.080–1.457), $P = 0.1293$] (Fig. 3). Second, the median OS (95 % CI) was 358.5 (274.0–458.0) days for six patients in the N-IRI group vs. 229.5 (58.0–387.0) days for eight patients in the IRI group [HR (95 % CI), 0.369 (0.110–1.242), $P = 0.0944$] (Fig. 3). Furthermore, at the 18-month follow-up, the RR in the EGFR 2+/3+ subgroup was 33.3 % for six patients in the N-IRI group vs. 0.0 % for six patients in the IRI group, and the DCR in the corresponding groups was 83.3 % and 33.3 %, respectively.

Pharmacokinetics

Pharmacokinetic analysis was conducted using data collected from 11 patients ($n = 6$ from the N-IRI group and $n = 5$ from the IRI group). The pharmacokinetic parameters of nimotuzumab were similar to those reported from a previous phase I study of nimotuzumab in Japanese patients with solid tumors [18].

Safety

Adverse events were reported in all the patients. Table 3 shows the incidence, by treatment group, of major adverse events occurring at a frequency of ≥15 % in at least one group. The most common adverse events (≥50 % in at least one group) were neutropenia, diarrhea, nausea, alopecia, decreased appetite, fatigue, and leukopenia. A rash occurred in 25.0 % (10/40) and 4.8 % (2/42) of patients in the N-IRI and IRI groups, respectively. There were no cases with severe (≥grade 3) skin toxicity, including severe rash. Grade 3 or higher adverse events were encountered in 77.5 % of patients in the N-IRI group and 64.3 % of patients in the IRI group. The most common grade 3 or higher adverse events (≥10 % in at least one group) were neutropenia, nausea, leukopenia, anemia, pneumonia, and decreased hemoglobin. The two pneumonia-related deaths in the N-IRI group were considered to be causally related to the study drug. All patients with pneumonia were evaluated by an Independent Data Monitoring Committee to detect pneumonitis. However, no cases of pneumonitis were identified.

The incidence of adverse events resulting in discontinuation of irinotecan was 15.0 % (6/40) in the N-IRI group and 16.7 % (7/42) in the IRI group, with no significant difference between the two groups. The

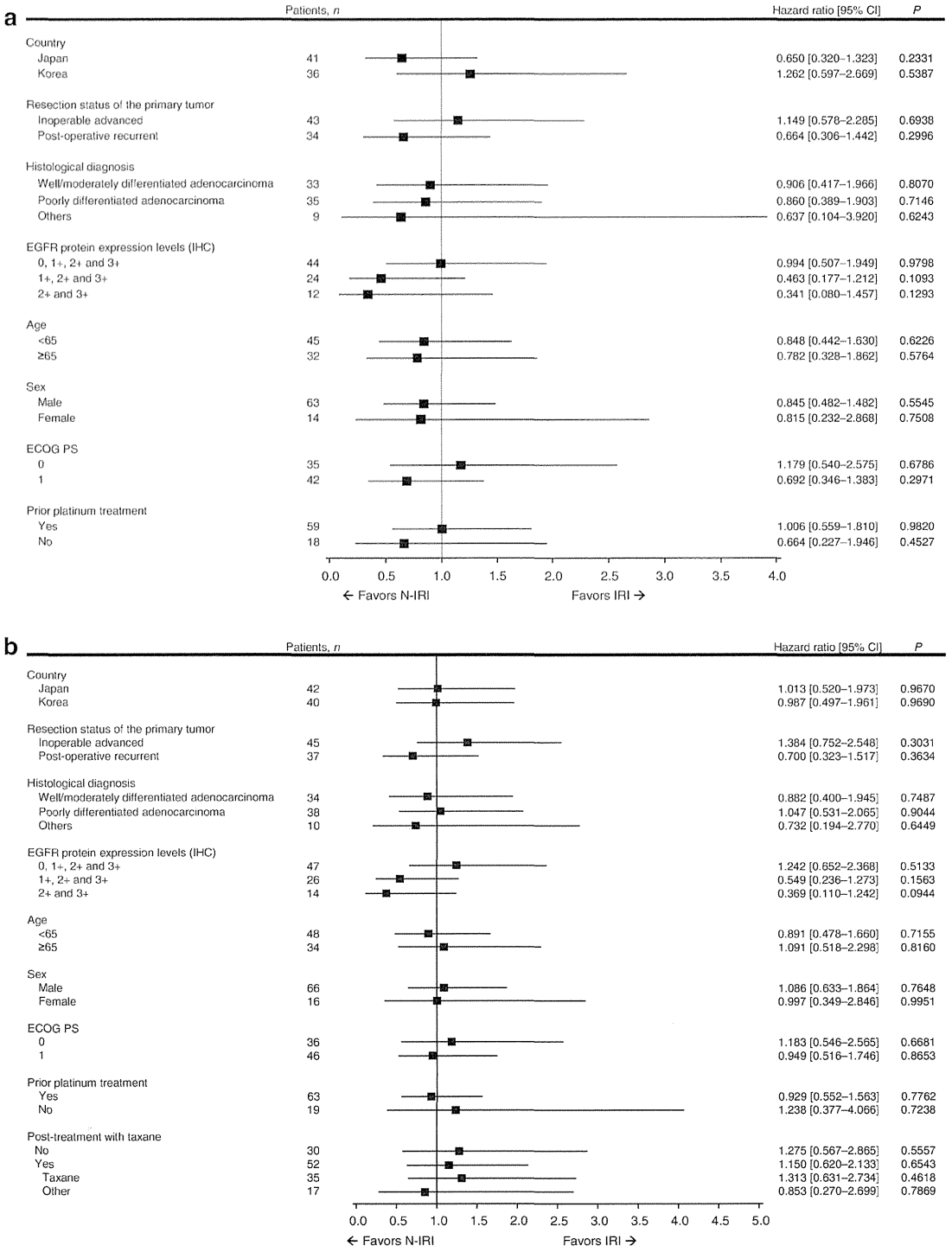

Fig. 3 Subset forest plots for progression-free survival (**a**) and overall survival (**b**). *N-IRI* nimotuzumab plus irinotecan, *IRI* irinotecan alone, *EGFR* epidermal growth factor receptor, *IHC* immunohistochemistry, *ECOG* Eastern Cooperative Oncology Group, *PS* performance status

incidence of adverse events resulting in discontinuation of nimotuzumab was 7.5 % (3/40) in the N-IRI treatment group.

Adverse events were reported for all patients in the EGFR 2+/3+ subgroup, and no significant difference was found in the frequency of adverse events between the IRI

Table 3 Adverse events occurring at an incidence of ≥ 15 % in each treatment arm

Adverse event	N-IRI (n = 40)				IRI (n = 42)			
	All grades		≥Grade 3		All grades		≥Grade 3	
	n	%	n	%	n	%	n	%
Infections and infestations								
Pneumonia	8	20.0	4	10.0	1	2.4	0	0.0
Blood and lymphatic system disorders								
Anemia	7	17.5	5	12.5	4	9.5	3	7.1
Leukopenia	20	50.0	6	15.0	15	35.7	4	9.5
Lymphopenia	7	17.5	3	7.5	4	9.5	0	0.0
Neutropenia	29	72.5	18	45.0	23	54.8	16	38.1
Thrombocytopenia	1	2.5	0	0.0	7	16.7	3	7.1
Metabolism and nutrition disorders								
Hypoalbuminemia	7	17.5	0	0.0	5	11.9	1	2.4
Decreased appetite	22	55.0	3	7.5	26	61.9	3	7.1
Gastrointestinal disorders								
Abdominal pain	14	35.0	0	0.0	14	33.3	3	7.1
Constipation	12	30.0	0	0.0	12	28.6	0	0.0
Diarrhea	25	62.5	3	7.5	25	59.5	2	4.8
Nausea	25	62.5	6	15.0	25	59.5	4	9.5
Stomatitis	6	15.0	0	0.0	5	11.9	0	0.0
Vomiting	17	42.5	3	7.5	13	31.0	2	4.8
Skin and subcutaneous tissue disorders								
Alopecia	23	57.5	0	0.0	15	35.7	0	0.0
Rash	10	25.0	0	0.0	2	4.8	0	0.0
General disorders and administration site conditions								
Asthenia	7	17.5	1	2.5	9	21.4	1	2.4
Fatigue	21	52.5	3	7.5	15	35.7	3	7.1
Pyrexia	8	20.0	0	0.0	13	31.0	0	0.0
Investigations								
Alanine aminotransferase increased	8	20.0	1	2.5	6	14.3	1	2.4
Aspartate aminotransferase increased	7	17.5	1	2.5	7	16.7	1	2.4
Hemoglobin decreased	11	27.5	4	10.0	13	31.0	6	14.3
Weight decreased	12	30.0	2	5.0	8	19.0	0	0.0

Number of patients, incidence of adverse events, and incidence of grades 3–5 adverse events

N-IRI nimotuzumab plus irinotecan, *IRI* irinotecan alone, *n* number of patients

and N-IRI groups in the EGFR 2+/3+ subgroup analysis. The incidence of adverse events in the EGFR 2+/3+ subgroup was similar to that in all randomized patients. In the EGFR 2+/3+ subgroup, rash of grade 1 or 2 occurred in 50.0 % (3/6) and 0.0 % (0/8) of patients in the N-IRI and IRI groups, respectively.

Discussion

The primary endpoint of prolonged PFS was not achieved in this study, suggesting no significant benefit of N-IRI in non-biologically selected patients with AGC. This result is suggested by recent studies that evaluated the efficacy of anti-EGFR antibody administration to AGC patients who were not biologically selected. In two prospective randomized phase III studies (EXPAND, REAL-3) of cetuximab and panitumumab conducted in AGC patients, the primary endpoint could not be achieved [26, 27]. These negative results emphasize the need to identify the biological target before starting a large phase III study.

In a preclinical study, nimotuzumab showed marked antiproliferative, proapoptotic, and antiangiogenic effects against tumors showing EGFR overexpression [14–16]. We previously demonstrated that the effects of nimotuzumab on human NSCLC cell lines were highly dependent on EGFR status [28]. Nimotuzumab inhibited EGFR phosphorylation in cancer cells with high/moderate surface expression of EGFR, but not in those with low surface EGFR expression. Immunoblot analysis showed inhibition of EGFR phosphorylation in H292 and Ma-1 cells expressing high and moderate levels of EGFR on the cell surface, but not in H460, H1299, and H1975 cells showing a low level of surface EGFR expression [28].

In a clinical study of head and neck cancer to assess the efficacy of nimotuzumab in combination with radiotherapy, a controlled, double-blind, randomized clinical trial was conducted. For EGFR-positive patients, a significant survival improvement was detected for nimotuzumab-treated patients (OS, 16.5 months) compared with the control group (OS, 7.2 months) [29].

Nimotuzumab is a humanized IgG1 antibody-directed agent, meaning that EGFR should be considered as the first candidate for its biological target. In this study, subset analysis showed a median PFS of 118.5 days in the EGFR 2+/3+ subgroup of the N-IRI group and 59.0 days in the corresponding subgroup of the IRI group; the RR was 33.3 % and 0.0 %, respectively. Furthermore, there was no significant difference in the frequency and seriousness of adverse events between the IRI and N-IRI groups in the subset of EGFR 2+/3+ subgroup analysis. Submission of tissue samples was not mandatory, and EGFR protein expression was only detected for 57.3 % of the full analysis set population. Therefore, the subset analysis based on the EGFR status could not yield any conclusive results. However, the results seem to imply that nimotuzumab can improve PFS and OS in AGC patients with high EGFR expression levels (2+/3+) when administered in combination with irinotecan.

In our study, the further exploratory biomarker of *K-ras* mutations was measured in 48 patients, and only 2 patients

were found to harbor *K-ras* mutations. The *EGFR* gene copy number was measured in 46 patients, and 1 patient was detected with gene amplification. These results were consistent with previous reports [30, 31]. The roles of *K-ras* mutations and *EGFR* gene amplification were not clear in this study.

Recently, the ToGA study showed that the HER-2-targeting monoclonal antibody trastuzumab improved OS in AGC patients with HER-2 protein overexpression by IHC or gene amplification by FISH [10]. We also investigated the HER-2 expression levels by IHC and found that 14.6 % (7/48) of patients showed HER-2 2+/3+ expression and 29.2 % (14/48) of patients showed EGFR 2+/3+ expression. Only 2.1 % (1/48) of patients showed 2+/3+ expression of both EGFR and HER-2, suggesting there is little overlap between EGFR and HER-2 overexpression in gastric cancer [13]. Currently, targeted therapy for gastric cancer is limited to patients with HER-2 overexpression. However, in future, patients with gastric cancer showing EGFR overexpression might benefit from treatment with nimotuzumab.

In the present study, rash occurred in ten patients (25.0 %) in the N-IRI group, which represents a lower frequency than that reported for patients receiving other anti-EGFR monoclonal antibodies, such as cetuximab or panitumumab [26, 27]. Furthermore, there were no cases of severe (≥grade 3) skin toxicity in either treatment group. The frequency and severity of skin toxicity associated with nimotuzumab appears to be lower than that associated with other anti-EGFR antibodies. The safety profile of nimotuzumab could be expected to maintain good quality of life as well as compliance and shows potential for combination of nimotuzumab with irinotecan. The median relative dose intensity of irinotecan and nimotuzumab was 94.94 % and 96.55 %, respectively, in the N-IRI group. In the study of REAL-3, compliance with the baseline chemotherapy was decreased because of some severe toxicities, and the combination of a triple-chemotherapy regimen with panitumumab appears to be difficult to deliver [27].

The mechanism underlying this lower frequency of skin toxicity of nimotuzumab compared with that of other known anti-EGFR antibodies has been investigated in several recent studies [14–17, 19, 20]. These studies suggested that a low incidence of skin toxicity may be associated with the following: (1) the intermediate affinity ($K_d = 10^{-8}$ M) of nimotuzumab, which is at least one order of magnitude lower than that of cetuximab or panitumumab; and (2) the different binding profile of nimotuzumab, which requires bivalent binding for stable attachment to the cellular surface compared with that of cetuximab, which requires only monovalent binding [15, 16]. This finding implies that nimotuzumab binding to EGFR occurs only when the surface EGFR density is sufficiently high to allow bivalent binding. Tumor cells overexpressing EGFR are common, allowing for selective binding of nimotuzumab.

In conclusion, although the primary endpoint of prolonged PFS was not met in our study, subset analysis showed that the N-IRI regimen may have potential to improve PFS and OS in EGFR 2+/3+ patients. An open-label, randomized phase III trial comparing N-IRI and IRI in EGFR 2+/3+ AGC patients is currently ongoing.

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