Panel: Research in context

Systematic review

Combination chemotherapy is the cornerstone of treatment of small-cell lung cancer (SCLC). We searched PubMed for reports of randomised clinical trials published in English up to Sept 30, 2013, using the terms "lung neoplasms", "small-cell lung cancer", "radiotherapy", and "not non-small-cell lung cancer". We also searched the reference lists of retrieved articles. The quality of evidence was assessed mainly on the basis of whether the standard chemotherapy regimen, etoposide plus cisplatin, was used as the reference group. Meta-analyses[3,4] have shown that addition of thoracic radiotherapy to combination chemotherapy significantly improves the survival of patients with limited-stage SCLC. Several randomised trials[5–7] have shown that early use of concurrent thoracic radiotherapy is better than sequential or late use, when etoposide and cisplatin are used as combination chemotherapy. The US intergroup phase 3 study[8] showed that accelerated hyperfractionated thoracic radiotherapy (AHTRT) with etoposide plus cisplatin for limited-stage SCLC was better than standard fractionation, once-daily irradiation.

Interpretation

At present, standard treatment for patients with limited-stage SCLC is etoposide plus cisplatin with thoracic radiotherapy. AHTRT is recommended when logistically acceptable. As far as we are aware, JCOG0202 is the first randomised trial investigating the efficacy of irinotecan plus cisplatin in patients with limited-stage disease. The hypothesis that irinotecan plus cisplatin could improve overall survial for these patients compared with etoposide plus cisplatin was refuted. Four cycles of etoposide plus cisplatin and concurrent AHTRT should be the standard of care in patients with limited-stage SCLC, and discouragement and cessation of tobacco use is still the most effective strategy to reduce deaths from SCLC.

irinotecan plus cisplatin group than in the etoposide plus cisplatin group; grade 3 or 4 diarrhoea was more frequent in the irinotecan plus cisplatin group than in the etoposide plus cisplatin group (table 2).

Late radiation morbidity after thoracic irradiation did not differ between the two groups (two [1·6%] grade 3 and two [1·6%] grade 4 events in the etoposide plus cisplatin group *vs* two [1·6%] grade 3 events in the irinotecan plus cisplatin group). Only one event [1·3%] of nausea of grade 3 due to prophylactic cranial irradiation was reported in the etoposide and cisplatin group.

Study treatment was terminated because of side-effects in 17 patients (13%) in the etoposide plus cisplantin group and in 26 patients (20%) in the irinotecan plus cisplatin group. There were three treatment-related deaths. One treatment-related death from pneumonitis occurred 86 days after induction chemoradiotherapy (induction etoposide plus cisplantin plus AHTRT). The patient was not randomised because a diffuse interstitial shadow occurred after 28·5 Gy of AHTRT. One patient in the etoposide plus cisplantin group died of radiation pneumonitis 116 days after completion of study treatment. One patient in the irinotecan plus cisplatin group died of brain infarction during the third course of consolidation chemotherapy.

Discussion

In this study of 258 patients with limited-stage SCLC, three cycles of irinotecan plus cisplatin did not improve overall survival compared with three cycles of etoposide plus cisplatin, after one cycle of etoposide plus cisplatin with concurrent AHTRT (panel). Randomisation was done after completion of induction chemoradiotherapy, thus the findings are unlikely to be biased by induction chemoradiotherapy.

JCOG previously reported the results of a randomised phase 3 trial[9] (JCOG9511) comparing irinotecan plus cisplatin versus etoposide plus cisplatin for extensive-stage SCLC. Median overall survival was 12·8 months and 19·5% patients were alive at 2 years in the irinotecan plus cisplatin group, whereas in the etoposide plus cisplatin group, median overall survival was 9·4 months only 5·2% of patients were alive after 2 years (p=0·002 from unadjusted log-rank test). Similar trials[13–15] done mainly in white patients with extensive-stage SCLC, including the Southwest Oncology Group trial[13] (S0124) using almost the same eligibility criteria and identical treatment regimens as JCOG9511, did not confirm the JCOG results. These results suggest pharmacogenomic differences between Japanese and non-Japanese patients.[16] Despite several negative trials, two meta-analyses[17,18] using non-individual-patient data showed a significant survival improvement with irinotecan compared with etoposide in patients with extensive-stage SCLC. However, the efficacy of irinotecan plus cisplatin shown in extensive-stage SCLC was not observed in the Japanese patients with limited-stage SCLC in our current study.

Side-effects were as expected. Severe non-haematological adverse events were much the same between the two groups, except for grade 3 or 4 diarrhoea which occurred in 10% of patients in the irinotecan plus cisplatin group and only 2% of patients in the etoposide plus cisplatin group. Late radiation reactions were not increased in the irinotecan plus cisplatin group. 86% of patients in the irinotecan plus cisplatin group received the planned three cycles of consolidation chemotherapy, and 90% received three cycles in the etoposide plus cisplatin group. Thus, compliance does not explain the negative results in the present study.

5-year overall survival in patients who received standard etoposide plus cisplatin plus concurrent AHTRT has been reported to be 24–26% in two phase 3 studies[7,8] in limited-stage SCLC. Although we failed to show an improvement in survival with our investigational regimen, the 5-year overall survival of 34·3% for all patients in the present study would be the best outcome reported so far. The 5-year overall survival of 55·3% in women who received standard etoposide plus cisplatin consolidation therapy is encouraging. This favourable result might be attributable to selection of patients, such as inclusion of patients with ECOG performance status of 0 or 1, and aged 70 years or younger. However, this selection bias does not fully explain the difference because the proportion of patients with ECOG performance status of 2 in other trials was only about 5%.[7,8] Radiotherapy quality control undertaken in the present study might have contributed to the improved

outcome, because radiotherapy protocol deviations are associated with overall mortality.[11,19] Optimum care of patients, including full disclosure of prognosis in the consent form for the study, might be another factor related to the favourable outcome.[20,21]

Full dose irinotecan cannot be combined with radiotherapy.[22] Thus, it is unlikely that the addition of irinotecan to radiotherapy improves the outcome of patients with limited-stage SCLC who receive combined chemotherapy and radiotherapy treatment. In future trials, new active agents with radiosensitising potential are needed. Testing of different radiotherapy regimens would be another option to improve outcomes in limited-stage SCLC. A randomised trial to establish whether administration of high-dose thoracic radiotherapy, 70 Gy (2 Gy once daily over 7 weeks) or 61·2 Gy (1·8 Gy once daily for 16 days followed by 1·8 Gy twice daily for 9 days), will improve survival compared with 45 Gy (1·5 Gy twice daily over 3 weeks) is underway in the USA (NCT00632853).

At the present time, the results of our study indicate that four cycles of etoposide plus cisplatin plus concurrent AHTRT should continue to be the standard of care in patients with limited-stage SCLC. Because SCLC is strongly smoking-related, discouragement and cessation of tobacco use is still the most effective strategy to reduce deaths from SCLC.[23]

Contributors

TT was the chief investigator of the trial. KK, TH, SI, MN, MK, AY, FI, KT, SN, MH, HO, NY, TShin, HS, KM, KN, NS, and TT designed the trial and wrote the protocol. KK, TH, MN, MK, AY, FI, KT, SN, MH, HO, NY, TShin, HS, KM, KN, and TT enrolled patients. JM and TShib were responsible for data management, statistical analysis, and data interpretation. KK drafted the report. All authors were involved in writing the report and approved the final version.

Conflicts of interest

KK has received honoraria and a research grant from Daiichi-Sankyo. TT has received honoraria from Daiichi-Sankyo and Bristol-Myers Squibb. KN has received honoraria from Bristol-Myers Squib, Nippon Kayaku, and Daiichi-Sankyo. All other authors declare that they have no conflicts of interest.

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PHASE II STUDIES

Pemetrexed and carboplatin followed by pemetrexed maintenance therapy in chemo-naïve patients with advanced nonsquamous non-small-cell lung cancer

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Summary *Introduction* This study prospectively evaluated the efficacy and safety of pemetrexed and carboplatin followed by maintenance pemetrexed in chemo-naïve patients with advanced nonsquamous non-small cell lung cancer (NSCLC). *Methods* A total of 109 patients received pemetrexed (500 mg/m^2) and carboplatin (area under the curve = 6 mg/mL·min) every 21 days. For patients without disease progression after 4 cycles, pemetrexed was continued until disease progression or unacceptable toxicity. Pre-planned subgroup analysis results based on the presence of epidermal growth factor receptor (*EGFR*) mutations are also presented. *Results* The median number of treatment cycles was 5 (range: 1–30) in the entire study period. Most of the grade ≥3 toxicities observed were hematologic in nature, with no increase in

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the relative incidence associated with continuation maintenance therapy with pemetrexed. Among the 106 total patients assessable for efficacy, the objective response rate was 35.8 %, median progression free survival (PFS) 5.7 months, and median overall survival (OS) 20.2 months. Sixty patients received maintenance pemetrexed (median: 4 cycles, range: 1–26 cycles); median PFS from the beginning of induction treatment was 7.5 months. From the subgroup analysis for *EGFR* mutation status, the median OS of *EGFR* wild-type patients (n=61) was 20.2 months. *Conclusions* Pemetrexed/carboplatin followed by pemetrexed was well tolerated and active for front-line treatment of advanced nonsquamous NSCLC. Encouraging survival outcomes were observed even in *EGFR*-wild type patients.

Keywords Pemetrexed · Carboplatin · Continuation maintenance · Nonsquamous NSCLC · *EGFR* mutation status

Introduction

Lung cancer is the most common type of cancer globally and the leading cause of cancer death [1]. Approximately 85 % of patients with lung cancer have non-small cell lung cancer (NSCLC), and 70 % of NSCLC is inoperable, locally advanced, or metastatic [2]. Currently, nonsquamous histology has been an important determinant for clinical outcome in NSCLC patients treated with pemetrexed or bevacizumab chemotherapy [3–8]. In addition, oncogenic driver mutations, such as *EGFR* mutation and fusions of echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK), were found in a subset of patients with nonsquamous NSCLC. A higher proportion of tumors harboring *EGFR* mutations were reported in East Asian compared with Caucasian patients [9]. While some molecular-targeted agents, such as gefitinib, erlotinib and crizotinib, have dramatically improved overall survival in the population harboring these targetable oncogenic gene alterations, prognosis of the other wild-type patients with NSCLC remains to be improved [10–16].

Pemetrexed, a potent multitargeted antifolate, inhibits thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase, all of which are involved in the *de novo* synthesis of purines or pyrimidines [17]. Pemetrexed is the key drug in the treatment for nonsquamous NSCLC patients, showing consistently superior efficacy compared with standard treatments [4–7]. Recently, a new treatment paradigm using pemetrexed for continuation maintenance therapy after 4 cycles of pemetrexed/cisplatin has been reported in a large phase III trial [18]. Continuation maintenance therapy with pemetrexed improved PFS and OS in patients with advanced nonsquamous NSCLC compared with placebo.

While pemetrexed/cisplatin followed by pemetrexed maintenance therapy is the standard treatment in nonsquamous NSCLC, carboplatin-based regimens have been widely used as a substitute for cisplatin-based regimens due to their lower toxicity and more convenience for administering in outpatient treatment settings. However, clinical outcomes of continuation therapy with pemetrexed following pemetrexed in combination with carboplatin have not fully been addressed. This study was conducted to evaluate efficacy, including the survival outcome and safety of pemetrexed/carboplatin combination therapy followed by continuation maintenance with pemetrexed in chemo-naïve patients with advanced nonsquamous NSCLC. Given that *EGFR* mutation status has recently become a key factor for the overall treatment plan of advanced NSCLC, we also assessed the efficacy data according to the *EGFR* mutation status using a pre-planned analysis.

Materials and methods

Eligibility

Patients 20 years of age or older with histologically or cytologically confirmed advanced NSCLC, other than predominantly squamous cell histology, were eligible for the study. Each patient was required to have clinical stage IIIB, stage IV or recurrent disease, a lesion not amenable to curative radiation, and no history of prior chemotherapy [19]. Eligibility stipulated an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate function of the lungs, bone marrow, liver, and kidneys. The criteria for organ function specified baseline resting arterial oxygen saturation (SpO_2) on room air ≥93 %; hemoglobin ≥9.0 g/dL, white blood cells ≥3000/mm^3, neutrophils ≥1500/mm^3, platelets ≥100,000/mm^3, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤2.5 times upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, creatinine ≤1.5 times ULN, and 24-h creatinine clearance or calculated creatinine clearance ≥45 mL/min as estimated by the Cockcroft and Gault formula. Patients were required to have a life expectancy of at least 12 weeks and no brain metastases other than stable, asymptomatic, or treated metastatic brain tumors. This study was conducted following good clinical practices and the ethical principles outlined in the Declaration of Helsinki. This study protocol was approved by the institutional review board at each participating center. All patients signed written informed consent before enrollment. The trial has been registered under the number NCT 01020786.

Study design and treatment

This was an open-label, multicenter, single arm, prospective postmarketing study. The primary objective was to evaluate

the efficacy, as measured by PFS, of this study treatment in patients with advanced nonsquamous NSCLC who received at least one dose of the initial combination therapy. Secondary endpoints, including OS, disease control rate (DCR), overall response rate (ORR), and safety, were also evaluated.

Eligible patients received pemetrexed 500 mg/m^2 through a 10-min intravenous infusion followed by intravenous infusion of carboplatin at a dose corresponding to target area under the curve (AUC) equal to 6 mg/mL·min (AUC6) over at least 30 min on day 1. This combination therapy was repeated every 21 days for up to 4 cycles. After 4 cycles, patients with complete response (CR), partial response (PR), or stable disease (SD) received maintenance therapy with pemetrexed 500 mg/m^2 every 21 days until evidence of disease progression or development of unacceptable toxicities. All patients received oral folic acid (0.5 mg) daily and a vitamin B_{12} (1 mg) injection every 9 weeks, beginning at least 1 week before the first dose and continuing until 3 weeks after the last dose of study treatment.

Subsequent cycles of treatment were withheld until the following criteria were satisfied: neutrophil count ≥1500/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥8.0 g/dL, ECOG performance status ≤1, SpO_2 ≥93 %, AST/ALT ≤2.5 times ULN, total bilirubin ≤1.5 times ULN, and 24-h creatinine clearance or calculated creatinine clearance ≥45 mL/min as estimated by the Cockcroft and Gault formula, other tolerable nonhematologic toxicity, and a decision by the physician. If these criteria were not satisfied within 29 days from the date of dose administration in the cycle because of adverse events, the pemetrexed dose was reduced from 500 to 400 mg/m^2 or from 400 to 300 mg/m^2, and the carboplatin dose was reduced from AUC6 to an AUC of 5 mg/mL·min (AUC5) or from AUC5 to an AUC of 4 mg/mL·min (AUC4). Any patient who required a third dose reduction was withdrawn from the study. In addition, if the next cycle had not started within 43 days from previous dosing due to toxicity, the patient was discontinued.

Baseline and treatment assessments

Baseline evaluations included medical history, physical examination, electrocardiogram, tumor status, ECOG performance status, clinical laboratory test, and *EGFR* mutation status. Testing for *EGFR* mutations was outsourced from each institution to commercial clinical laboratories in Japan. Computed tomography was performed for tumor assessment within 21 days of initiation of study treatment and was repeated every 6 weeks thereafter. All responses were defined according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, version 1.0. If a patient was documented as having a CR or a PR, a confirmatory evaluation was performed after an interval of at least 4 weeks. The patient was considered to have SD if it was confirmed and sustained for 6 weeks or longer after the start of study treatment. PFS was defined as the time from enrollment to the date of confirmation of progressive disease (PD) or the date of death from any cause (whichever occurs earlier). Patients who received any subsequent systemic anticancer therapy prior to objective PD or death would be censored at the date of the last objective progression-free disease assessment prior to starting the subsequent systemic anticancer therapy. Overall survival was defined as the time from enrollment until death from any cause. For patients with unknown death status, OS would be censored at the last date the patient was known to still be alive.

Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Statistical methods

The sample size of 100 patients had a power of 90 % at a one-sided type I error rate of 0.05 to compare PFS of this study regimen versus the first-line platinum-based combination therapy as a constant value under the following assumptions: the expected PFS of the first-line therapy of platinum-based combination regimen was 5 months, the expected PFS of this study treatment was 7 months, the enrollment period was 8 months, and the follow-up period was 12 months.

Efficacy and safety analyses were planned to be performed on patients who received at least one dose of the treatment. Since some patients had significant protocol violations during the study, they were excluded from the efficacy analysis prior to the database lock. In this manuscript, the efficacy was assessed on the latter data set.

Time-to-event variables were analyzed using Kaplan-Meier estimation techniques, including Kaplan-Meier curves, quartiles, and interval estimation using 90 % and 95 % confidence intervals (CIs). For DCR and ORR, 95 % CIs were calculated using the exact test. Prespecified subgroup analyses for PFS and ORR based on *EGFR* mutation status were also included.

Results

Patient characteristics

Patient disposition is shown in Fig. 1. Between December 2009 and July 2010, 111 patients with recurrent or newly diagnosed, advanced nonsquamous NSCLC were enrolled at 25 clinical sites in Japan. Two patients were subsequently discontinued from the study for not meeting entry criteria, and 109 patients received the study treatment. Baseline characteristics are summarized in Table 1. The median age for the treated population was 63 years (range: 38–78 years), and 40 patients (36.7 %) were female. Other key characteristics at baseline included

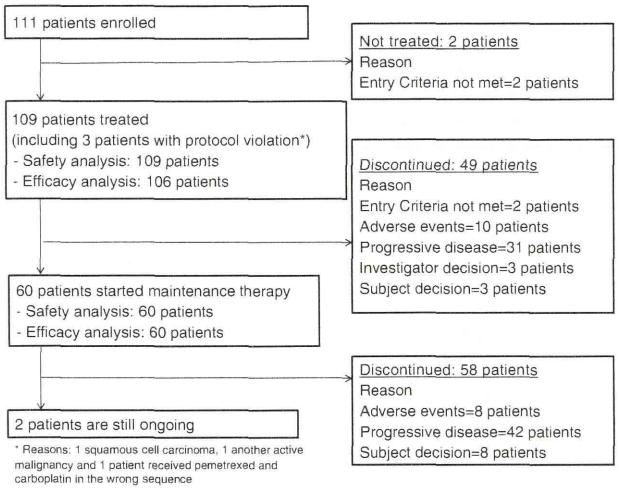

Fig. 1 Patient disposition

adenocarcinoma histology (97.2 %) and stage IV disease (66.1 %).

Treatment delivery

Patients received a median of 5 cycles (range: 1–30) of treatment in the entire study period, with 75 patients (68.8 %) completing at least 4 cycles. After completion of 4 cycles of carboplatin and pemetrexed combination therapy, 60 patients (55.0 %) continued pemetrexed monotherapy with a median of 4 cycles (range: 1–26) in the maintenance period. The remaining 15 patients did not receive pemetrexed maintenance therapy due to disease progression (8 cases), adverse events (4 cases), investigator decision (2 cases), or patient decision (1 case).

Overall, 30 patients (27.5 %) out of 109 experienced dose reductions, and 66 patients (60.6 %) experienced dose delay due to adverse events, mainly due to myelosuppression. Among the 60 patients in the maintenance period, 10 patients (16.7 %) had a dose reduction, and 33 patients (55.0 %) had a dose delay due to toxicities.

Table 1 Patient characteristics

Characteristics	N=109	%
Age (yr)		
Median	63	–
Range (min, max)	38–78	–
Gender (n)		
Male	69	63.3
Female	40	36.7
Performance status (n)		
0	37	33.9
1	72	66.1
Disease stage (n)		
IIIB	33	30.3
IV	72	66.1
Recurrence	4	3.7
Histology (n)		
Adenocarcinoma[a]	106	97.2
Large cell lung carcinoma	3	2.8
EGFR mutation status (n)		
Positive	24	22.0
Negative	63	57.8
Unknown	3	2.8
Not done	19	17.4

[a] One patient's tumor was reclassified as squamous cell carcinoma after study entry, and the examination of *EGFR* gene type was not done

Efficacy

Out of 109 patients, 106 were evaluable for efficacy analysis. Three patients were excluded for the following reasons: revised diagnosis of squamous cell carcinoma during the study (1 patient), diagnosis of another active malignancy (1 patient), and delivery of pemetrexed and carboplatin in the wrong sequence during the initial combination period (1 patient). There were 38 partial responses and no complete responses, yielding an ORR of 35.8 % (95 % CI: 26.8 %–45.7 %) (Table 2). Forty-one patients (38.7 %) had stable disease, yielding an overall DCR (CR + PR + SD) of 74.5 % (95 % CI: 65.1 %–82.5 %) (Table 2). At the median follow-up period of 18.5 months (range: 2.1–24.4 months), the median PFS and OS were 5.7 months (95 % CI: 4.4–7.3 months) and 20.2 months (95 % CI: 16.7 months–not calculable), respectively (Table 2 and Fig. 2).

Among 60 patients who received continuation maintenance with pemetrexed, the median PFS from the beginning of induction treatment was 7.5 months (95 % CI: 6.5–8.3 months); median OS was not calculable, with a 1-year survival rate of 89.7 %. In the 46 patients who discontinued study treatment before receiving pemetrexed maintenance, on the other hand, the median PFS was 2.8 months (95 % CI: 2.2–3.0 months), median OS was 8.6 months (95 % CI: 5.7–14.3 months) and 1-year survival rate was 46.8 %.

Sub-group analysis: *EGFR* mutation status

In the present study, *EGFR* mutation status was evaluated in 85 (80 %) of 106 patients evaluable for efficacy; 24 patients harbored an activating *EGFR* gene mutation, whereas 61 patients were *EGFR* wild-type. We prospectively performed subgroup analysis of efficacy according to *EGFR* mutation status. The ORR in the patients with and without *EGFR* mutations were 37.5 % (95 % CI: 18.8 %–59.4 %) and 36.1 % (95 % CI: 24.2 %–49.4 %), respectively (Table 2). The median PFS was 5.7 months (95 % CI: 5.2–7.2 months)

Table 2 Treatment outcome

		EGFR mutation	
Entire period	Total (*N*=106)	Positive (*N*=24)	Negative (*N*=61)
Median PFS, mo	5.7	5.7	6.9
95 % CI	4.4–7.3	5.2–7.2	4.3–7.8
Median OS, mo	20.2	Not calculable	20.2
95 % CI	16.7–Not calculable	20.2–Not calculable	14.2–Not calculable
Overall best response, *n* (%)			
Complete response	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	38 (35.8)	9 (37.5)	22 (36.1)
Stable disease	41 (38.7)	8 (33.3)	27 (44.3)
Progressive disease	20 (18.9)	3 (12.5)	10 (16.4)
Not evaluable	7 (6.6)	4 (16.7)	2 (3.3)
Overall response rate, *n* (%)	38 (35.8)	9 (37.5)	22 (36.1)
95 % CI	26.8–45.7	18.8–59.4	24.2–49.4
Disease control rate, *n* (%)	79 (74.5)	17 (70.8)	49 (80.3)
95 % CI	65.1–82.5	48.9–87.4	68.2–89.4

CI confidence interval, *PFS* progression-free survival, *mo* month(s), *OS* overall survival

for *EGFR* mutation-positive patients and 6.9 months (95 % CI: 4.3–7.8 months) for *EGFR* wild-type patients (Table 2). At the time of analysis, the median OS was not calculable for *EGFR* mutation-positive patients, but 1-year survival rate was 95.7 %; the median OS of patients with *EGFR* wild-type tumors was 20.2 months (95 %CI: 14.2 months-not calculable) with a 1-year survival rate of 68.1 % (Table 2 and Fig. 3a). In *EGFR* wild-type patients, the median OS of those who were treated with pemetrexed continuation maintenance (*n*=37) was notably longer compared with that of 24 patients who did not continue pemetrexed maintenance, whereas OS results in the patients who harbored *EGFR* activating mutation were similar among those with (*n*=14) or without (*n*=10) maintenance therapy using pemetrexed (Fig. 3b).

Safety

All 109 patients who received the initial combination therapy were assessable for safety analysis. The major adverse events for each treatment period (entire, initial combination, and maintenance periods) are shown in Table 3. Hematologic toxicities reaching ≥ grade 3 were neutropenia (56.0 %), thrombocytopenia (41.3 %), anemia (29.4 %), and leukopenia (22.0 %). Nonhematologic toxicities observed in more than half of patients included appetite loss (75.2 %), nausea (74.3 %), fatigue (67.9 %), and ALT increased (51.4 %), but the incidence of toxicities of grade 3 or higher was less than 10 %. The majority of adverse events were observed during the initial 4 cycles of pemetrexed and carboplatin combination therapy. Common toxicities ≥ grade 3 observed in the maintenance period were similar to those observed during the initial combination treatment period, including neutropenia (38.3 %), thrombocytopenia (16.7 %), leukopenia (11.7 %), and anemia (10.0 %). Newly emerged or deteriorated toxicities during maintenance periods were rarely observed. No treatment-related deaths were reported in this study.

Discussion

This was a prospective, multicenter clinical study of first-line combination therapy with pemetrexed and carboplatin followed by maintenance therapy with pemetrexed in chemo-naive patients with advanced nonsquamous NSCLC. This regimen achieved a response rate of 35.8 %, median PFS of 5.7 months, and median OS of 20.2 months. Although the lower limit of one-sided 95 % CI of PFS seen in this trial (4.4 months) did not exceed the prior assumption of a median PFS of 5.0 months, the survival results were striking. Since patients with *EGFR*-mutation positive advanced NSCLC had dramatically improved survival outcomes following treatment with *EGFR* tyrosine kinase inhibitors, the proportion of such patients in this trial may have had an impact on this favorable survival outcome [10–14]. However, the median OS of 20.2 months in 61 *EGFR* wild-type patients was much longer than expected [13], which was still encouraging.

Our study also confirmed findings from an earlier phase II study which showed excellent tolerability of the pemetrexed/carboplatin combination as a first-line chemotherapy [20]. Similarly, our study supported both the safety of

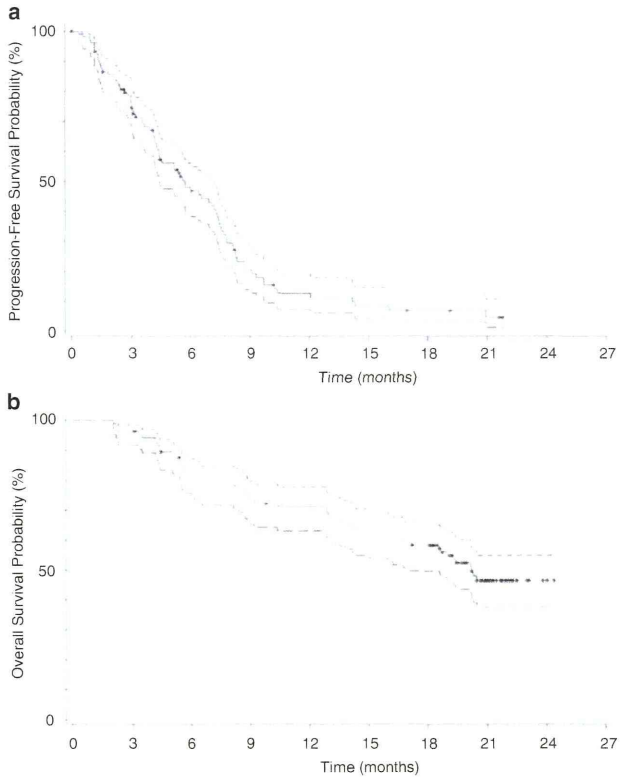

Fig. 2 **a.** Kaplan-Meier curves for progression-free survival curve (*solid line*) with 95 % confidence band (*dashed lines*). **b.** Kaplan-Meier curves for overall survival curve (*solid line*) with 95 % confidence band (*dashed lines*)

pemetrexed and carboplatin as an initial therapy for advanced nonsquamous non-small-cell lung cancer, and also the feasibility of pemetrexed as a maintenance therapy in these patients. The most common hematologic toxicity reaching grades 3 or 4 was neutropenia, but febrile neutropenia occurred in only 1 case. Grade 3 or 4 thrombocytopenia was also frequently observed and 7.3 % of patients received platelet transfusion. However, this condition was considered manageable without any severe bleeding events. There was also no increase in the incidence of hematologic toxicities associated with continuation maintenance with pemetrexed. With regard to nonhematologic toxicity, there were no grade 3 or 4 toxicities encountered in >10 % of patients throughout the study treatment. No unexpected toxicities were observed.

Pemetrexed is used in the maintenance setting for advanced nonsquamous NSCLC, following the results of the PARAMOUNT study, in which continuation maintenance therapy with pemetrexed following induction therapy with pemetrexed/cisplatin resulted in significantly improved PFS and OS [18, 21]. In the present study, the favorable tolerability profile of pemetrexed maintenance after induction of pemetrexed/carboplatin is reflected in the observation that 55 % of patients were able to continue on pemetrexed monotherapy with a median of 4 cycles. The median PFS of 7.5 months from the beginning of induction treatment in 60 patients who received maintenance therapy with pemetrexed is consistent with the finding of the PARAMOUNT study where a median PFS of 6.9 months was achieved by continuation maintenance with pemetrexed [18]. Although there are limitations when comparing results from different studies, these data suggest that pemetrexed continuation maintenance therapy is effective whether cisplatin or carboplatin is used for the induction chemotherapy. In our ad-hoc exploratory analyses, *EGFR* wild-type patients who continued with pemetrexed as a maintenance therapy demonstrated marked OS compared with those who did not receive maintenance therapy, whereas there was no obvious difference in OS of 24 *EGFR*-mutation positive patients, regardless of maintenance treatment. Given that most these patients (10 of 14 patients with pemetrexed maintenance, 9 of 10 patients without maintenance) received gefitinib or erlotinib as poststudy treatment, a good outcome could have been achieved in patients harboring the targetable oncogenic gene alterations by subsequent treatment with these active therapies, even though they did not continue pemetrexed maintenance. Although this study was not a

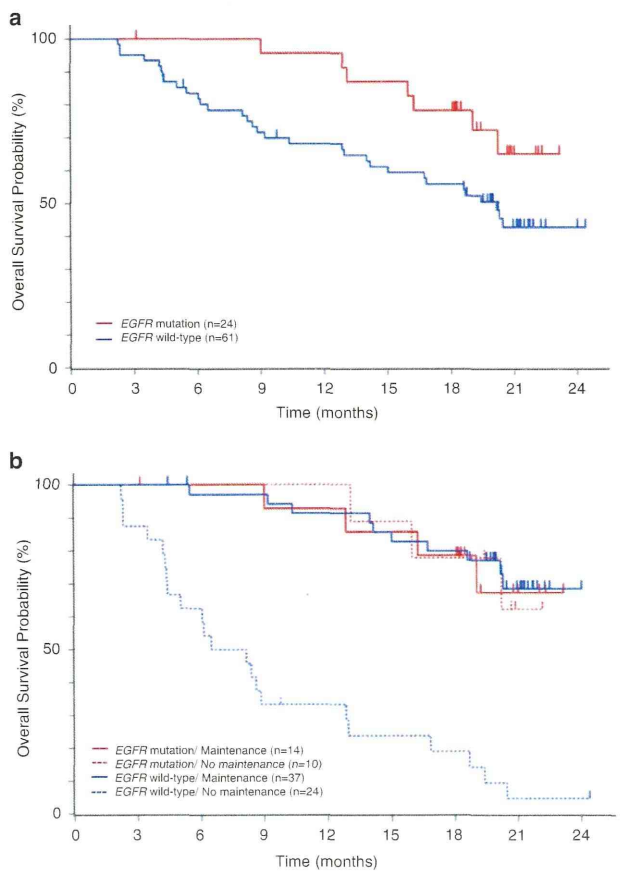

Fig. 3 **a.** Overall survival by EGFR mutation status. **b.** Overall survival by EGFR mutation status and maintenance-treated status

Table 3 Toxicity by treatment period

	Entire period (N=109)			Initial combination period (N=109)			Maintenance period (N=60)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Hematologic	*n*(%)	*n*(%)	*n* (%)	*n*(%)	*n* (%)	*n* (%)	*n* (%)	*n*(%)	*n* (%)
Leukopenia	83 (76.1)	24 (22.0)	–	82 (75.2)	23 (21.1)	–	43 (71.7)	7 (11.7)	–
Neutropenia	86 (78.9)	47 (43.1)	15 (13.8)	84 (77.1)	45 (41.3)	14 (12.8)	44 (73.3)	21 (35.0)	3 (5.0)
Thrombocytopenia	94 (86.2)	30 (27.5)	15 (13.8)	94 (86.2)	30 (27.5)	15 (13.8)	40 (66.7)	10 (16.7)	–
Anemia	98 (89.9)	32 (29.4)	2 (1.8)	98 (89.9)	31 (28.4)	2 (1.8)	52 (86.7)	8 (13.3)	–
	Any Grade	Grade ≥3		Any Grade	Grade ≥3		Any Grade	Grade ≥ 3	
Non-hematologic	*n* (%)	*n* (%)		*n* (%)	*n* (%)		*n* (%)	*n* (%)	
Appetite loss	82 (75.2)	6 (5.5)		81 (74.3)	6 (5.5)		21 (35.0)	–	
Nausea	81 (74.3)	1 (0.9)		80 (73.4)	1 (0.9)		21 (35.0)	–	
Vomiting	42 (38.5)	3 (2.8)		42 (38.5)	3 (2.8)		4 (6.7)	–	
Fatigue	74 (67.9)	2 (1.8)		69 (63.3)	2 (1.8)		33 (55.0)	–	
Rash	32 (29.4)	1 (0.9)		29 (26.6)	1 (0.9)		6 (10.0)	–	
Fever	22 (20.2)	1 (0.9)		20 (18.3)	1 (0.9)		3 (5.0)	–	
Alopecia	8 (7.3)	–		8 (7.3)	–		3 (5.0)	–	
Neuropathy	10 (9.2)	–		7 (6.4)	–		5 (8.3)	–	
ALT increased	56 (51.4)	7 (6.4)		49 (45.0)	5 (4.6)		30 (50.0)	3 (5.0)	
AST increased	55 (50.5)	2 (1.8)		43 (39.4)	1 (0.9)		34 (56.7)	1 (1.7)	

ALT alanine aminotransferase, *AST* aspartate aminotransferase

randomized trial, these results may stimulate further interest in the clinically relevant efficacy of pemetrexed maintenance in *EGFR* wild-type patients for whom the limited therapeutic options exist.

In conclusion, this study regimen of pemetrexed/carboplatin followed by pemetrexed maintenance is feasible and effective as a first-line treatment for advanced nonsquamous NSCLC patients. Our findings have strengthened the rationale for the ongoing randomized phase III trial comparing this regimen with the carboplatin, paclitaxel and bevacizumab combination in patients with advanced, nonsquamous NSCLC [22].

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