experienced disease relapse outside the thorax and within the thorax, respectively. Two patients experienced disease relapse both within and outside the thorax. The most common first failure organ was the brain (five patients, 42%).

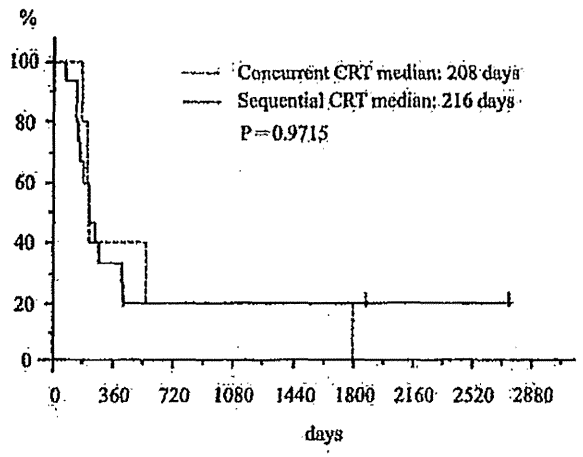

Figure 1. Kaplan–Meier curves for the progression-free survival (PFS) of patients aged 75 years or older treated with concurrent chemoradiotherapy (CRT) and sequential CRT are shown (concurrent CRT, red dashed line; sequential CRT, blue continuous line). The median PFS was 208 days in concurrent CRT and 216 days in sequential CRT. There was no statistically significant difference between the two groups (log-rank $P = 0.9715$).

Table 5 shows the adverse events in these 12 patients. Although there were moderate levels of hematological toxicities, gastrointestinal toxicities tended to be mild. It is noteworthy that Grade 3 or more severe pneumonitis occurred in four patients (33%).

DISCUSSION

Our investigation is important as it includes a considerable number of LD-SCLC patients aged 75 years or older who have been treated with CRT. Moreover, as this study documents a precise clinical course (i.e. treatment response, PFS, OS, treatment compliance and adverse events), it will enable physicians to determine the optimal treatment strategy for this category of patients.

Two previous research papers have detailed clinical course data in studies similar to ours. In one study, seven LD-SCLC patients aged 75 years or older were treated with etoposide plus cisplatin or carboplatin and with concurrent TRT (14). TRT treatment was delayed for more than 7 days in three of the seven patients. Three experienced Grade 3 or more severe febrile neutropenia, and three experienced

Table 4. Adverse events in patients treated with concurrent CRT and sequential CRT

	Concurrent chemoradiotherapy ($n = 5$)						Sequential chemoradiotherapy ($n = 15$)					
	Gr 1	Gr 2	Gr 3	Gr 4	≥Gr 3 (%)	All (%)	Gr 1	Gr2	Gr 3	Gr 4	≥Gr 3 (%)	All (%)
Leukopenia	0	0	3	2	100	100	1	6	8	0	53	100
Neutropenia	0	0	0	5	100	100	1	0	3	11	93	100
Anemia	0	4	1	0	20	100	3	7	2	0	13	80
Thrombocytopenia	2	2	1	0	20	100	6	3	3	1	27	87
Fatigue	1	1	1	0	20	60	7	2	0	0	0	60
Anorexia	2	1	1	0	20	80	6	5	0	0	0	73
Constipation	2	2	0	0	0	80	12	1	0	0	0	87
Nausea	2	2	0	0	0	80	6	1	0	0	0	47
Infection	0	2	0	0	0	40	1	1	1	0	7	20
Febrile neutropenia	0	0	3	0	60	60	0	0	2	0	13	13
Bilirubin	1	0	0	0	0	20	2	1	0	0	0	20
AST	0	0	0	0	0	0	2	0	0	0	0	13
ALT	1	0	0	0	0	20	3	0	0	0	0	20
Hyponatremia	2	0	0	1	20	60	4	0	1	1	13	40
Creatinine elevation	1	0	0	0	0	20	3	2	0	0	0	33
Pneumonitis	4	0	0	0	0	80	7	0	3	1	27	73
Esophagitis	1	3	1	0	20	100	5	4	0	0	0	60
Dermatitis	4	0	0	0	0	80	9	0	0	0	0	60
Eruption	2	0	0	0	0	40	1	1	0	0	0	13

Gr, grade; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

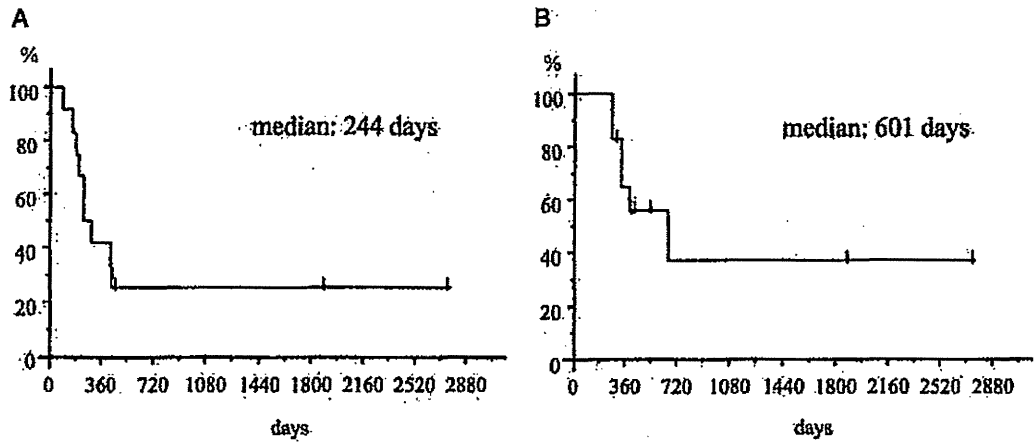

Figure 2. The Kaplan–Meier curve for the PFS (A) and overall survival (OS) (B) of 12 patients aged 75 years or older, treated with etoposide plus carboplatin followed by sequential thoracic radiotherapy is shown. The median PFS and OS were 244 and 601 days, respectively.

Table 5. Adverse events in patients treated by etoposide plus carboplatin and sequential radiotherapy, $n = 12$

	Gr 1	Gr 2	Gr 3	Gr 4	≥Gr 3 (%)	All (%)
Leukopenia	0	6	6	0	50	100
Neutropenia	0	0	3	9	100	100
Anemia	2	5	2	0	17	75
Thrombocytopenia	4	3	2	1	25	83
Fatigue	5	2	0	0	0	58
Anorexia	5	4	0	0	0	75
Constipation	9	1	0	0	0	83
Nausea	5	0	0	0	0	42
Infection	1	1	1	0	8	25
Febrile neutropenia	0	0	2	0	17	17
Bilirubin	1	1	0	0	0	17
AST	1	0	0	0	0	8
ALT	3	0	0	0	0	25
Hyponatremia	3	0	0	0	0	25
Creatinine elevation	2	2	0	0	0	33
Pneumonitis	5	0	3	1	33	75
Esophagitis	5	3	0	0	0	67

Grade 4 thrombocytopenia. One patient died due to radiation pneumonitis and this was judged as treatment-related death. In the second study, the outcome of elderly patients aged 70 years or older, five of whom were 75 years or older, who received early concurrent CRT with four cycles of etoposide plus cisplatin, was reported (15). Of the 12 patients in this report, 8 (67%) experienced Grade 3 or more severe febrile neutropenia. Of the five patients aged 75 years or older, three could not complete the four cycles of chemotherapy and all five experienced delayed TRT for more than 7 days. In our study, five patients received concurrent CRT and two could not complete the chemotherapy course due to toxicities. TRT was discontinued in one patient and another experienced delayed TRT for more than 7 days due to toxicities. These patients suffered from prolonged toxicities and their quality of life decreased for a long time. Moreover, it is speculated that fitter patients were treated by concurrent CRT and more fragile patients were treated by sequential CRT. Therefore, it is suggested that concurrent CRT is not feasible for all LD-SCLC patients aged 75 years or older. Moreover, a high frequency of discontinuation, dose reduction and omission of chemotherapy/TRT in concurrent CRT may lead to a similar PFS as that achieved with sequential CRT.

Based on the previous Phase III study which investigated chemotherapeutic regimen for elderly or poor-risk patients with ED (extensive disease)-SCLC (16) and the convenient administration schedule of carboplatin, etoposide (80 mg/m^2) on days 1–3 plus carboplatin (AUC 5) on day 1 followed by sequential TRT 45Gy in twice-daily fractions or 50 Gy in a once-daily fraction was the most frequently used treatment method for LD-SCLC patients aged 75 years or older in our institute. In our study, the major adverse events of etoposide plus carboplatin followed by sequential TRT were hematological toxicities, including neutropenia and thrombocytopenia. Gastrointestinal toxicities such as anorexia, nausea, vomiting and constipation were very mild. All of the toxicities were manageable and no treatment-related death occurred. The response rate, OS and PFS were satisfactory, when taking the patients' characteristics in our study and the results of the previous Phase II studies that evaluated CRT for LD-SCLC patients aged 70 years or older, into account (17, 18). However, as Grade 3 or more severe pneumonitis occurred in 4 of 12 patients (33%) similar to a retrospective subset analysis of LD-SCLC patients treated with etoposide plus cisplatin and concurrent early CRT in a Phase III trial (10), attention should be paid to the occurrence of radiation

pneumonitis. It may be appropriate to set the radiation field based on the tumor volume after induction chemotherapy to reduce the frequency and severity of radiation pneumonitis (19). On the other hand, the previous Phase III study have also shown etoposide plus split doses of cisplatin seems to be another standard chemotherapeutic regimen for elderly or poor-risk patients with ED-SCLC (16). Etoposide plus split doses of cisplatin on days 1–3 followed by sequential TRT could be a candidate for the standard treatment of LD-SCLC patients aged 75 years or older. However, because only three patients were treated by etoposide plus split doses of cisplatin on days 1–3 followed by sequential TRT, it is hard to lead a definitive conclusion in this study.

Our study has a few limitations. The intervals between evaluations for lesions in this study were not as accurate as those in a prospective study. The severity of non-hematological toxicities, in particular, may have been underestimated in the present study due to its retrospective nature. Patients were treated as inpatients during most of the treatment period, and the toxicity data were recorded in detail in the patients' medical records. The sample size in this study is not very large; therefore, it is difficult to reach a definitive conclusion. However, as it is not easy to collect data on a large number of LD-SCLC patients aged 75 years or older who have received CRT, this study may be useful for physicians trying to determine the optimal treatment strategy for LD-SCLC patients aged 75 years or older.

In conclusion, it is suggested that concurrent CRT is not feasible for all LD-SCLC patients aged 75 years or older. Etoposide (80 mg/m^2) on days 1–3 plus carboplatin (AUC 5) on day 1 followed by sequential TRT is one of the candidates for the standard treatment of these elderly LD-SCLC patients. A further prospective clinical trial is warranted to develop and evaluate the optimal treatment method for LD-SCLC patients aged 75 years or older.

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Conflict of interest statement

None declared.

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Original Article

A Phase 3 Study of Induction Treatment With Concurrent Chemoradiotherapy Versus Chemotherapy Before Surgery in Patients With Pathologically Confirmed N2 Stage IIIA Nonsmall Cell Lung Cancer (WJTOG9903)

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BACKGROUND: This study sought to ascertain whether induction concurrent radiotherapy added to chemotherapy could improve the survival of patients undergoing surgery for stage IIIA N2 nonsmall cell lung cancer (NSCLC). **METHODS:** Patients with pathologically proven N2 disease were randomized to receive either induction chemotherapy (docetaxel 60 mg/m^2 and carboplatin AUC [area under the receiver operating characteristic curve] = 5 for 2 cycles) plus concurrent radiation therapy (40 Gy) followed by surgery (CRS arm) or induction chemotherapy followed by surgery (CS arm). They subsequently underwent pulmonary resection when possible. **RESULTS:** Sixty patients were randomly assigned between December 2000 and August 2005. The study was prematurely terminated in January 2006 because of slow accrual. The most common toxicity was grade 3 or 4 leukopenia in 92.9% of patients in the CRS arm and 46.4% in the CS arm. Induction therapy was generally well tolerated and there were no treatment-related deaths in either arm. Downstaging in the CS arm and CRS arm was 21% and 40%, respectively. The progression-free survival (PFS) and overall survival (OS) in the CS arm were 9.7 months and 29.9 months (PFS, hazard ratio [HR] = 0.68; P = .187), and those in the CRS arm were 12.4 months and 39.6 months (OS, HR = 0.77; P = .397), respectively. The PFS with and without downstaging was 55.0 and 9.4 months, respectively (HR = 3.39; P = .001). The OS with and without downstaging was 63.3 and 29.5 months, respectively (HR = 2.62, P = .021). **CONCLUSIONS:** The addition of radiotherapy to induction chemotherapy conferred better local control without significant adverse events. Tumor downstaging is important for prolonging the OS in patients with stage IIIA (N2) NSCLC. *Cancer* 2012;118:6126-35. © *2012 American Cancer Society.*

KEYWORDS: induction therapy before surgery, phase 3 study, carboplatin, docetaxel, stage IIIA nonsmall cell lung cancer.

Lung cancer is the leading cause of cancer death in most industrialized countries. Nonsmall cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers. One-third of patients with NSCLC are found to have locally advanced tumors (stage IIIA or IIIB) at the time of initial diagnosis. Pulmonary resection remains the only accepted mode of therapy and hope for potential cure in patients with early stage I or II NSCLC. However, patients with stage IIIA, N2 disease are at substantial risk of recurrence and death even after complete surgical resection. The resectability of patients with stage III locally advanced lung cancer is only 14% to 20%, and the corresponding 5-year survival rate ranges from

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13% to 36%.[1,2] When pathologic involvement of the mediastinal lymph nodes is documented prior to surgical resection, a high rate of both local and distant failure with resection alone has provided the rationale for a combined modality approach consisting of induction chemotherapy or chemoradiotherapy before surgery. Induction therapy has several theoretical advantages,[3] such as increasing the sensitivity of tumors in early-stage disease, decreasing the tumor volume to enable better local control in subsequent surgery, faster eradication of clinically undetected micrometastatic disease, and better patient tolerance and compliance compared with postsurgery treatments.

With regard to preoperative chemotherapy for stage IIIA lesions with mediastinal lymph node metastasis, 5 randomized clinical trials of induction chemotherapy prior to surgery have been conducted.[4-8] Two of these studies involved small cohorts (n = 60) that included mainly stage IIIA, N2 disease, and showed a significant survival advantage associated with induction chemotherapy compared with surgery alone.[5,6] None of the other trials reported any beneficial outcome for bimodality therapy compared with surgery alone.[4,7,8]

Induction treatment using combined concurrent chemoradiotherapy prior to surgery resulted in NSCLC cure rates of 30% to 40% at 5 years and appeared to improve survival over treatment with surgery alone.[9-11] We conducted a phase 2 trial of induction chemoradiotherapy before surgery in 22 patients with stage IIIA NSCLC who have pathologically proven mediastinal lymph node metastasis.[12] The chemotherapy regimen used was cisplatin and etoposide, and the radiation dosage was 40 Gy. The response rate was 64% and the 5-year survival rate was 41%. Subsequently, we conducted a phase 2 study of induction chemoradiotherapy before surgery in 40 early stage NSCLC (stage IB, II).[13] Carboplatin (AUC = 5), and docetaxel (60 mg/m^2) were administered once every 3 weeks for 2 cycles concurrent with 40 Gy radiation. In patients with no evidence of disease progression, thoracotomy was performed 3 to 5 weeks later. All the patients completed induction chemoradiotherapy, and 39 patients underwent thoracotomy and were completely resected. There were no treatment-related deaths, and estimated 5-year survival was 69.9%. Induction concurrent chemotherapy (carboplatin plus docetaxel) with 40 Gy of thoracic radiotherapy was considered to be feasible and tolerable. Based on the findings of these 2 previous phase 2 trials, we planned a phase 3 study in which patients with pathologically documented stage IIIA (N2) NSCLC were randomized to either an induction chemotherapy followed by surgery (CS) arm, or an induction-concurrent chemoradiotherapy followed by surgery (CRS) arm. The primary endpoint of this trial was the overall survival rate at 5 years.

MATERIALS AND METHODS

Eligibility

The present study was undertaken at multiple academic and community hospitals in Japan. The 6th edition of the TNM staging system was used to stage the lung cancers using a computed tomography (CT) scan of the chest and upper abdomen; bone scan; and CT or magnetic resonance imaging (MRI) scan of the brain. Inclusion criteria were stage IIIA (pN2) disease: T1, T2, or T3 primary NSCLC with pathological proof of N2 disease (from biopsy samples of the ipsilateral mediastinal nodes that were visible on a CT scan). The size of the metastatic mediastinal lymph node was more than 1 cm along the short axis. Patients were assessed together by a thoracic surgeon, a radiation oncologist, and a medical oncologist or pulmonologist to establish whether N2 disease was present to the extent that concurrent chemotherapy and radiotherapy were indicated instead of definitive resection. It was also necessary to determine whether each lesion was potentially resectable. Additional inclusion criteria were measurable disease as defined by the World Health Organization (WHO), an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate hematologic, hepatic, cardiac, renal (serum creatinine $\leq$ 1.5 mg and creatinine clearance $\geq$ 40 mL/hour), and pulmonary functions (including partial pressure of arterial oxygen [PaO_2] $\geq$ 70 Torr, forced expiratory volume in 1 second [$FEV_{1.0}$] $\geq$ 1.5 L). The exclusion criteria were prior malignancy other than nonmelanoma skin cancer or adequately treated stage I in situ cervical cancer, uncontrolled angina pectoris, a history of congestive heart failure or myocardial infarction within 3 months, pulmonary fibrosis detectable by CT scan, chronic obstructive pulmonary disease ($FEV_{1.0} \leq 65\%$), and greater than 10% weight loss within the previous 6 months.

All patients provided written informed consent after study approval by the institutional review board of each participating center.

Study Design and Treatment

In the current phase 3 multicenter trial, patients were randomly assigned on a 1:1 basis to an induction CS arm or an induction CRS arm (Fig. 1). The patients were then

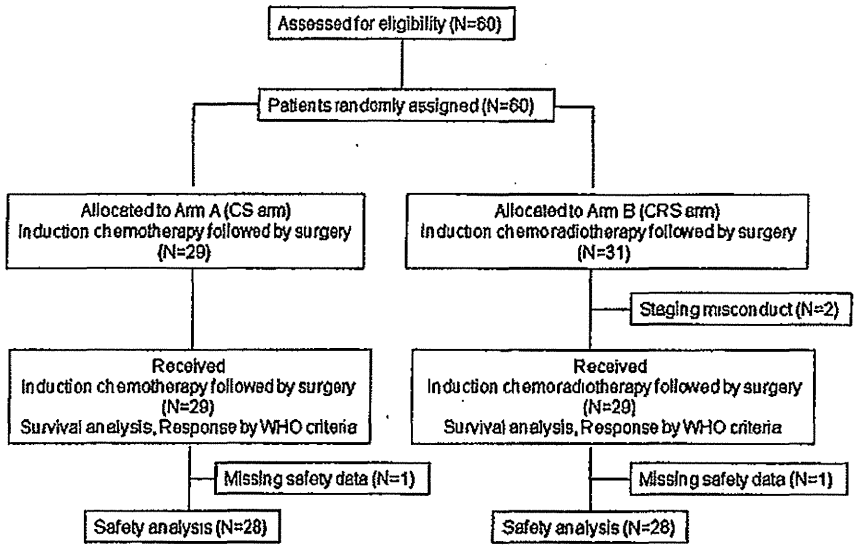

Figure 1. CONSORT diagram is shown for this study. CRS indicates concurrent chemoradiotherapy followed by surgery; CS, chemotherapy followed by surgery; WHO, World Health Organization.

stratified by sex, institution, and number of mediastinal lymph nodes. The induction chemotherapy involved 2 cycles of carboplatin (area under the receiver operating curve [AUC] = 5 on days 1, 22, intravenous infusions) and docetaxel (60 mg/m^2 on days 1, 22, intravenous infusions). Thoracic radiotherapy (40 Gy in 20 fractions of 2 Gy over 4 weeks) was also administered from day 1 in the CRS arm (Fig. 2)

All patients were treated with a linear accelerator photon beam of 6 MV or more. At the commencement of this multi-institutional study, a 3-dimensional (3D) treatment planning system using CT was not available at some of the participating institutions. Hence, 2-dimensional (2D) treatment planning techniques were allowed. Radiation doses were specified at the center of the target volume, and doses were calculated assuming tissue homogeneity without correction for lung tissues. The primary tumor and involved nodal disease received 40 Gy in 2 Gy fractions over 4 weeks via the anterior and posterior opposing portals. Radiation fields included the primary tumor with a margin of at least 1.0 cm, and the ipsilateral hilum and mediastinal nodal areas with a margin of 0.5 to 1.0 cm from the paratracheal lymph nodes (#2) to 4.5 cm below the tracheal bifurcation including subcarinal lymph nodes (#7). The contralateral hilum was not included. The supraclavicular areas were not treated routinely, but the ipsilateral supraclavicular area was treated when the primary tumor was located in the upper lobe.

The patients were reassessed using CT scan plus repeat pulmonary function tests 2 to 4 weeks after completion of the induction therapy. The response to induction was assessed by WHO criteria without the need for a second confirmation of response. If the disease had not progressed and the patient remained medically healthy, a complete surgical resection with a mediastinal lymph node dissection was performed 3 or 4 weeks after the induction therapy was completed. No consolidation chemotherapy was administered after surgery. Dose-reduction guidelines were specified in the protocol for both treatment arms. Patients in the CRS arm who could not be treated surgically within 6 weeks after induction therapy received further radiotherapy of up to 66 Gy in 33 fractions in total. In this boost radiotherapy procedure, the spinal cord was excluded from the radiation fields.

Patients were scheduled for a chest CT scan 4 to 6 weeks after completion of the last chemotherapy cycle and were followed up every 2 months for at least 5 years. During this time, the patients received CT scans of the chest and upper abdomen, CT or MRI scans of the brain, and bone scans every 6 months.

Statistical Methods

Analyses were performed by intention to treat, using only eligible patients. The primary endpoint was the survival rate at 5 years. Overall survival (OS) was defined as the time from randomization to death from any cause.

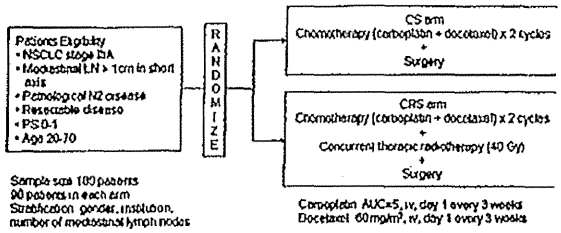

Figure 2. The study schema is shown. AUC, area under the receiver operating characteristic curve; CRS, concurrent chemoradiotherapy followed by surgery; CS, chemotherapy followed by surgery; iv, intravenous; LN, lymph node; NSCLC, nonsmall cell lung cancer; PS, performance status.

Secondary endpoints were the response rate and the toxicity of induction therapy, resectability rate, downstaging rate, death from any cause, operative morbidity, progression-free survival (defined as the time from randomization to disease progression), and patterns of failure. We calculated the sample size assuming a 2-sided log-rank test with a type I error rate of 0.05 and 80% statistical power, and a follow-up of 5 years.

The target sample size was 180 patients to detect a 20% absolute improvement in the CRS arm,[12] assuming 20% 5-year OS in the CS arm. Kaplan-Meier methods were used to estimate the median OS and PFS. The HRs and the 95% confidence intervals (CIs) were estimated using the Cox proportional hazards regression model, and the OS and PFS were analyzed using the log-rank test.

RESULTS

Patient Characteristics

Between December 2000 and August 2005, 60 patients were randomly assigned and 58 patients were treated. The 2 untreated patients (both in the CRS arm) did not satisfy the eligibility criteria and were excluded from the subsequent analyses. Because of the slow patient accrual, this study was terminated at 60 enrollments in accordance with a Data Safety and Monitoring Committee recommendation made in December 2005. Patient characteristics were well-balanced in terms of age, sex, histology, smoking history, and TNM stage. The chemotherapy cycles of induction therapy did not differ between the CS arm (mean 2 ± 0 standard deviation) and the CRS arm (mean 1.9 ± 0.3 standard deviation). Regarding the number of patients possessing multistation mediastinal lymph node metastases, there was no difference between the 2 arms ($P = .297$; Table 1).

Table 1. Patient Demographics

Characteristic	CS	CRS	*P*
Registered patients	29	31	
Median age (range), y	57.0 (36-70)	58.0 (34-68)	.947
Sex (M/F)	19/10	21/10	.855
Histology (adenocarcinoma/squamous carcinoma/other)	16/8/5	23/5/3	.422
Smoker/nonsmoker	22/7	23/8	.881
T 1/2/3	11/14/4	11/18/2	.577
N 0/1/2/3	0/0/29/0	0/0/30/1	.329
Lymph node station (single/multiple)	15/14	11/20	.297
M 0/1	29/0	30/1	1.000
Staging misconduct	0	2	
Survival analysis	29	29	
Missing safety data	1	1	
Safety data analysis	28	28	

Abbreviations: CRS, concurrent chemoradiotherapy followed by surgery; CS, chemotherapy followed by surgery.

The 25 patients (89%) in the CS arm and 20 patients (71%) in the CRS arm completed 2 cycles of chemotherapy at full dose. There was no difference in dose intensity of docetaxel and carboplatin between the 2 arms. Docetaxel dose intensity in each arm was as follows: 1.00 ± 0.00 (CS arm, first course), 0.99 ± 0.04 (CS arm, second course), 1.00 ± 0.00 (CRS arm, first course), 0.94 ± 0.08 (CRS arm, second course). Carboplatin dose intensity in each arm was as follows: 0.97 ± 0.16 (CS arm, first course), 0.95 ± 0.12 (CS arm, second course), 1.00 ± 0.00 (CRS arm, first course), 0.88 ± 0.14 (CRS arm, second course).

In the CRS arm, 28 of 29 patients received 40 Gy of radiation dose as scheduled and the remaining 1 patient received only 34 Gy because of neutropenic fever. A total of 77% of patients underwent 3D treatment planning radiation using computed tomography.

Treatment Efficacy

The tumor response for the induction therapy was 7 PRs, 19 NCs, 2 PDs in the CS arm, and 7 PRs, 19 NCs, 2 PDs in the CRS arm. Overall response rate was 25% in both arms. The number of patients who underwent surgery was 25 of 29 (86.2%) in the CS arm and 26 of 29 (89.7%) in the CRS arm. The reasons for patients not undergoing surgery were PD in 2 patients, no recovery of PS after chemotherapy in 1 patient, and patient refusal in 1 patient in the CS arm, and PD in 2 patients and no recovery from adverse events in 1 patient in the CRS arm. Postprotocol treatment of patients not undergoing surgery was radiotherapy in 2 patients, chemoradiotherapy in 1 patient, and best supportive therapy in 1 patient in the CS arm,

Table 2. Toxicity, From National Cancer Institute Common Toxicity Criteria, Version 2.0

Adverse Event	Chemotherapy + Surgery (n = 28)		Chemoradiotherapy + Surgery (n = 28)		P
	Grade 1 + 2	Grade 3 + 4	Grade 1 + 2	Grade 3 + 4	
Nausea	19 (67.9%)	0	21 (75.0%)	3 (10.7%)	.554
Vomiting	2 (7.1%)	0	7 (25.0%)	1 (3.6%)	.036
Fever	5 (17.9%)	0	14 (50.0%)	0	.011
Dyspnea	0	0	1 (3.6%)	0	.313
Infection	2 (7.1%)	2 (7.1%)	4 (14.3%)	1 (3.6%)	.716
Peripheral neuropathy	2 (7.1%)	0	1 (3.6%)	0	.553
Allergic reaction	1 (3.6%)	0	5 (17.9%)	0	.084
Dysphagia	0	0	9 (32.1%)	0	
Leukopenia	12 (42.9%)	13 (46.4%)	2 (7.1%)	26 (92.9%)	.075
Neutropenia	6 (21.4%)	21 (75.0%)	3 (10.7%)	25 (89.3%)	.313
Anemia	25 (89.3%)	0	24 (85.7%)	2 (7.1%)	.639
Thrombocytopenia	12 (42.9%)	0	19 (67.9%)	2 (7.1%)	.014
Increased transaminase	8 (28.6%)	0	12 (42.9%)	1 (3.6%)	.168
Increased creatinine	2 (7.1%)	0	7 (25.0%)	0	.089

and single-agent chemotherapy in 3 patients in the CRS arm. The downstaging rate was 20.8% (5 of 24, missing data 1 patient) in the CS arm and 40.0% (10 of 25, missing data 1 patient) in the CRS arm ($P = .215$). After downstaging, pTNM of patients in the CS arm was pT1N0M0, pT2N0M0, pT3N0M0, pT1N1M0, and pT2N1M0 in 1 patient each. On the contrary, pTNM of patients in CRS arm was T0N0M0 in 3 patients (pathologic complete response), T1N0M0 in 2 patients, T2N0M0 in 4 patients, and T2N1M0 in 1 patient. The surgical procedures used and the number of patients treated were as follows: lobectomy in 20, bilobectomy in 3, wedge resection plus segmentectomy in 1, and pneumonectomy in 1 (the CS arm); lobectomy in 23, bilobectomy in 1, and exploratory thoracotomy in 2 (the CRS arm).

Toxicity

Table 2 summarizes the toxicity characteristics among the treated patients. The most common toxicity was a grade 3 or 4 leukopenia in 26 patients (92.9%) in the CRS arm and 13 patients (46.4%) in the CS arm ($P = .075$). Grade 3 or 4 neutropenia was reported in 25 (89.3%) and 21 (75.0%) patients in the CS arm ($P = .313$). Grade 3 or 4 thrombocytopenia was reported in 2 patients (7.1%) in the CRS arm but was not observed in any patient in the CS arm. Among the nonhematological toxicities, grade 1 or 2 vomiting was reported in 7 (25.0%) cases in the CRS arm and in 2 (7.1%) in the CS arm ($P = .036$). Grade 1 or 2 fever was reported in 15 patients (50.0%) in the CRS arm and 5 (17.9%) in the CS arm ($P = .011$). Grade 1 or 2 dysphagia due to radiation was reported in 9 patients (32.1%) in the CRS arm. Other toxicities during induction therapy did not differ between the arms. No treatment-related deaths were reported throughout the trial in either arm.

Survival and First Relapse Site

Median follow-up times for surviving patients in the CS and CRS arms were 60.7 months (range 1.8 to 86.5 months) and 60.8 months (range 44.5 to 87.5 months), respectively. Progression-free survival (PFS) did not improve in the CRS arm versus the CS arm (median, 12.4 months vs 9.7 months; HR = 0.68 [95% CI = 0.38-1.21], $P = .187$; Fig. 3A). Overall survival (OS) also did not improve in the CRS arm versus the CS arm (median, 39.6 months vs 29.9 months; HR = 0.77 [95% CI = 0.42-1.41], $P = .397$; Fig. 3B). The 3-year survival rates in the CRS and CS arms were 51.7% and 39.3%, and the 3-year PFS rates were 34.5% and 17.9%, respectively. The median OS of patients with and without downstaging in the CRS arm was 72.1 months and 31.2 months, respectively (HR = 4.16 [95% CI = 1.16-14.93], $P = .018$). In the CS arm, these values were 32.6 months and 29.0 months, respectively (HR = 1.47 [95% CI = 0.424-5.09], $P = .542$). Exploratory analyses of all patients from both arms according to mediastinal downstaging showed that patients without downstaging (n = 35) had a median PFS of 9.4 months and a 3-year PFS rate of 14.3% (Fig. 4A). However, patients with downstaging (n = 15) had a significantly longer median PFS of 55.0 months and a 3-year PFS rate of 60.0% (HR = 3.39 [95% CI = 1.54-7.48], $P = .001$). In terms of the OS, patients without downstaging had a median OS of 29.5 months, with a 3-year survival rate of 40.0% (Fig. 4B). In contrast,

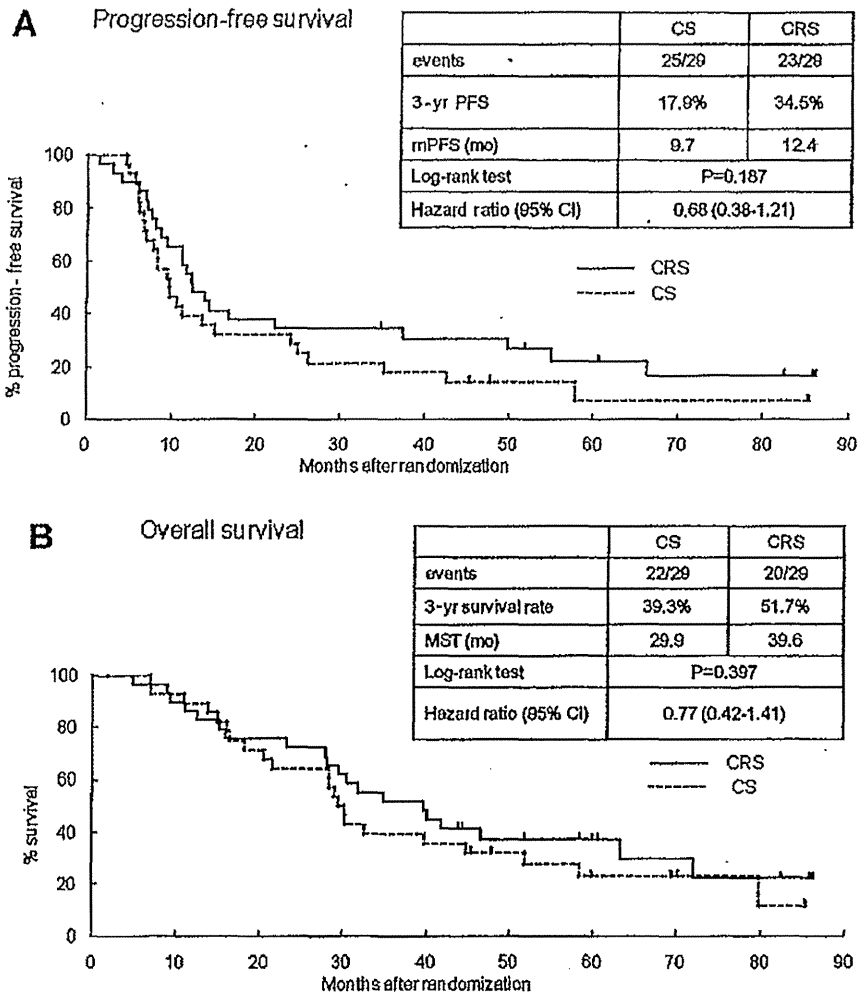

Figure 3. Curves are shown for (A) progression-free survival (PFS) and (B) overall survival analyses. CI, confidence interval; CRS, concurrent chemoradiotherapy followed by surgery; CS, chemotherapy followed by surgery; MST, median survival time.

patients with downstaging had a significantly longer OS of 63.3 months, with a 3-year survival rate of 66.7% (HR = 2.62 [95% CI = 1.12-6.09], $P = .021$).

Relapse was noted in 25 patients out of 28 in the CS arm (missing data 1) and in 24 out of 29 in the CRS arm. Local lymph node relapse in the CS arm and CRS arm occurred in 7 and 5 patients, respectively. Distant relapse occurred in 13 and 15 patients in the CS and CRS arms, respectively. Local and distant relapses occurred in 5 and 4 patients in the CS and CRS arms, respectively (Table 3). It is noteworthy that the brain and lung are the most frequent sites of distant metastasis (21 patients). One notable difference in the relapse pattern was the recurrence in the radiation field of the hilar and mediastinal lymph nodes. This was 41% (12 of 29 patients) in the CS arm, significantly higher than the 17% (5 of 29 patients) found in the CRS arm ($P = .0435$, chi-square test).

DISCUSSION

Our present study focuses on stage IIIA disease with pathologically proven mediastinal lymph node metastasis by investigating whether CRS would confer a better 5-year survival than CS. The observed trend was of a better OS and PFS in the CRS arm than in the CS arm. The median OS in the CRS and CS arms was 39.6 months

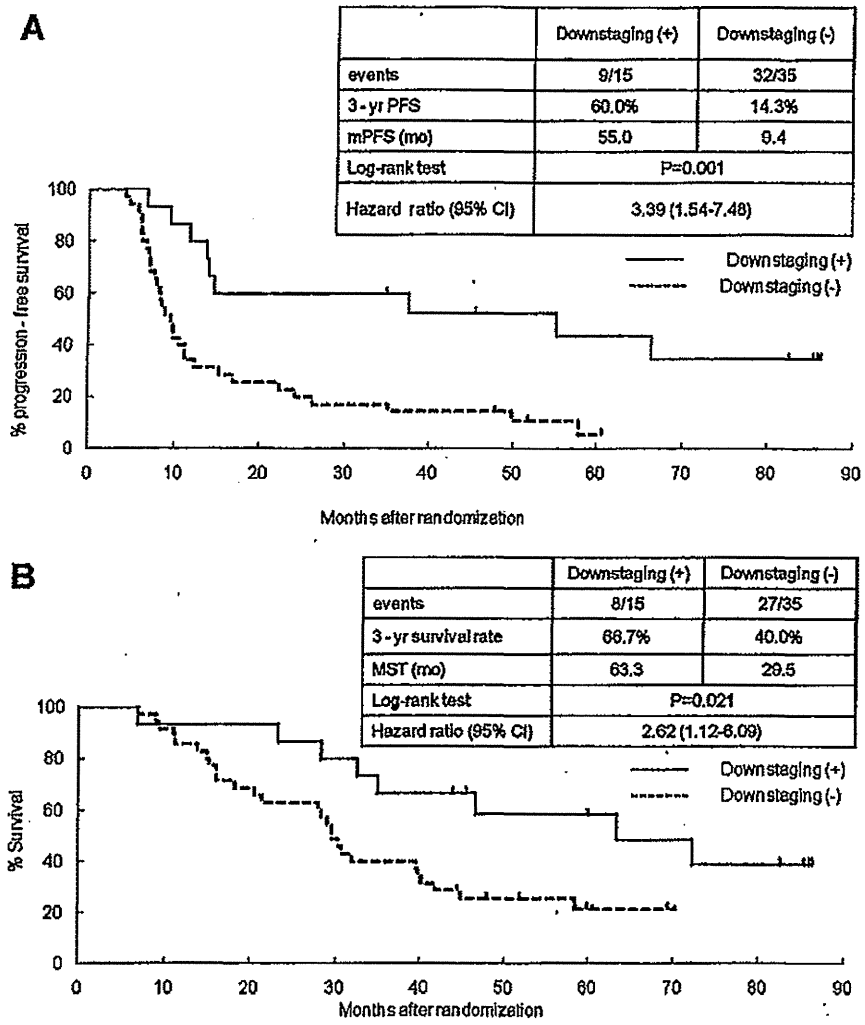

Figure 4. Curves are shown for (A) progression-free survival (PFS) and (B) overall survival of all resected patients according to downstaging. CI indicates confidence interval; CRS, concurrent chemoradiotherapy followed by surgery; CS, chemotherapy followed by surgery; MST, median survival time.

and 29.9 months, respectively. The median PFS in the CRS and CS arms was 12.4 months and 9.7 months, respectively. These differences are not statistically significant due to the small sample size. However, the median OS in the CRS arm in our study is clearly favorable compared with previous reports (13-32 months) in which patients with stage IIIA and IIIB disease were treated with preoperative chemoradiotherapy.[9-12] In particular, Albain et al recently reported a phase 3 study of concurrent chemoradiotherapy with or without surgical resection for stage IIIA, N2 NSCLC.[14] The median OS with and without surgery was 23.6 months and 22.2 months, respectively ($P = .24$) and the median PFS was better in patients with surgery (12.8 months vs 10.5 months, $P = .017$). In further exploratory analysis, the median OS was improved in the surgical group when a lobectomy was performed compared with a matched nonsurgical group (33.6 months vs 21.7 months, $P = .002$). However, the OS for patients in the pneumonectomy subgroup of the surgical cohort was not significantly poorer than that of the matched cohort in the nonsurgical group (18.9 months vs 29.4 months). A randomized study conducted by the German investigators directly compared CS with CRS in patients with stage IIIA-IIIB NSCLC.[15] The interventional-concurrent group

Table 3. First Relapse Site

Relapse Site	CS (n = 25)	CRS (n = 24)
Local	7	5
Hilar/mediastinal lymph node[a]	7	3
Supraclavicular lymph node	1	3
Distant	13	15
Lung	5	11
Bone	3	4
Liver	2	3
Brain	9	9
Para-aortic lymph node	0	2
Others	0	4
Local + distant	5	4
Hilar/mediastinal lymph node[a]	5	2
Supraclavicular lymph node	2	3
Lung	3	2
Bone	1	0
Pericardium	2	0
Brain	1	2
Others	2	0

Abbreviations: CRS, concurrent chemoradiotherapy followed by surgery; CS, chemotherapy followed by surgery.
[a] Recurrence in the radiation field.

was to receive 3 cycles of cisplatin and etoposide, followed by twice-daily radiation (total 45 Gy) with concurrent weekly carboplatin and vindesine, and then surgical resection. The control chemotherapy group was to receive 3 cycles of cisplatin and etoposide followed by surgery and then further radiotherapy. Of 524 eligible patients, 142 of 264 (54%) in the interventional group and 154 of 260 (59%) in the control group underwent surgery; 98 of 264 (37%) and 84 of 260 (32%) underwent complete resection. There was no significant difference according to the treatment group for PFS (intervention group: median 9.5 months vs control group: 10.0 months) or for OS (median 15.7 months vs 17.6 months). This may be due to the fact that they enrolled a substantial proportion of patients with a high disease burden (15% with T4N2 and 22% with T4N3).

Systemic chemotherapy is another neoadjuvant treatment modality that has been administered before surgery. The postsurgery OS in these cases was found to range from 20 to 28.7 months, and the 3-year survival rate ranged from 17% to 45%.[4-8] More recently, van Meerbeeck et al conducted a phase 3 trial that investigated the role of surgery versus radiotherapy after induction chemotherapy in 579 patients with pathologically documented stage IIIA, N2, NSCLC.[16] Patients received 3 cycles of platinum-based chemotherapy, and nonprogressors were then randomized for surgery (n = 164) or thoracic radiotherapy (n = 165). The median and 5-year OS values for patients assigned to the resection group versus the radiotherapy group were 16.4 versus 17.5 months and 15.7% versus 14%, respectively (HR = 1.06 [95% CI = 0.84-1.35]). However, the median OS was poorer than in our present study (39.6 months in the CRS arm) or in the study by Albain et al (23.6 months in chemoradiotherapy in the surgery arm).

The response rate from induction chemoradiotherapy in our study was relatively low (25%) and is poorer than the 59% to 74% reported for other concurrent chemoradiotherapy studies.[9-12] The most likely reason is that the period between induction therapy and surgery in our patients was short and shrinkage could not be confirmed in many cases, which resulted in a low response rate and a high stable disease rate (67.9%). Another possible reason is that in the present study we used a suboptimal preoperative radiation dose schedule (40 Gy in 20 fractions over 4 weeks). A better response rate is typically achieved following a higher radiation dose (45 Gy),[14] or hyperfractionated accelerated irradiation.[9-11,15,17,18] An exploratory analysis showed that the OS of our patients with downstaging (72.1 months) was significantly better than that of patients without downstaging (31.2 months) in the CRS arm ($P = .008$), although this survival benefit in patients with downstaging was not demonstrated in the CS arm ($P = .542$). Although the in-field recurrence was significantly higher in the CS arm compared with the CRS arm, this did not translate to better PFS or OS in the CRS arm because there was no significant difference of distant and distant + local recurrence between the 2 arms (CS vs CRS, 18/28; 64% vs 19/29; 65%). The number of patients having multistation lymph node disease in the CS arm was relatively high (14 of 29, 52%) compared with the CRS arm (11 of 31, 35%). This tendency might have led to low downstaging rate in the CS arm because irradiation has potent local control effect. The high downstaging rate and the absence of treatment-related death in our CRS arm translated into a longer median OS (39.6 months) and higher 3-year survival rate (51.7%). Choi et al[9] conducted a phase 2 study of an induction treatment involving twice-daily radiation and concurrent chemotherapy in 42 patients with stage IIIA NSCLC, and reported that the 5-year survival rate in patients with pathological complete response (79%) was significantly higher ($P = .04$) than that in patients with pN1 (42%) or pN2

(15%). In addition, Betticher et al[19] conducted a multicenter phase 2 trial of the efficacy of neoadjuvant docetaxel-cisplatin in 90 patients with NSCLC who had locally advanced N2 disease. Using multivariate analyses, they demonstrated that mediastinal clearance (downstaging rate: 60%, $P = .0003$,) and complete resection ($P = .0006$) were strong prognostic factors. These data indicate that, in patients with stage IIIA NSCLC, downstaging in mediastinal lymph nodes significantly improves the survival outcome. Small sample size and low downstaging rate appear to be reasons why the same tendency was not observed in our patients in the CS arm. Downstaging may be related to a chemotherapy regimen and chemotherapy cycles delivered, because cisplatin is generally more effective than carboplatin in inducing tumor shrinkage, and tumor response is most efficacious at 3 cycles of chemotherapy.[20]

Induction chemotherapy or chemoradiotherapy in our present trial was well tolerated by patients in both arms, with excellent treatment compliance. No grade 3/4 fever was found in either arm, despite the high incidence of grade 3/4 neutropenia (75% in the CS arm, 89.3% in the CRS arm), nor was any grade 3/4 radiation esophagitis observed in the CRS arm. Conversely, grade 3/4 esophagitis has been recorded in 8% to 53% of patients where radiation was delivered in a hyperfractionated accelerated fashion.[9-11,17,18] More importantly, no treatment-related deaths were observed in either arm in our trial during the induction and postoperative periods. Lobectomies may be safely performed following induction therapy, whereas pneumonectomy, especially on the right, may carry an unacceptable rate of perioperative mortality.[14,15] The appropriate selection of patients to undergo resection following induction therapy is thus critical.

Our study was prematurely terminated because of poor accrual rate. We assume several reasons for poor accrual. The first reason was stage migration that upgraded former stage IIIA disease to stage IV disease due to more frequent usage of brain MRI and positron emission tomography in staging. Hence, the number of stage IIIA N2 patients is not as large as a decade ago. The second reason was the difference of definition of resectability between thoracic surgeons and pulmonary physicians (or medical oncologists). The third reason was the preference of surgeons and/or medical oncologists to treat their patients with more effective chemoradiotherapy in terms of local control. The final reason was the reluctance of some thoracic surgeons to carry out preoperative chemoradiotherapy due to the possibilities of postsurgical complications. This theme of induction therapy before surgery is extremely vital, and therefore we will have to overcome poor accrual in future randomized phase 3 trials. To accomplish the trial, it is very important to perform diagnostic procedures such as mediasitinoscopy, thoracoscopy, or bronchofiberscopic transbronchial biopsy. We also need to establish less toxic chemotherapy regimens such as carboplatin plus paclitaxel or platinum compounds plus pemetrexed, adopt less toxic radiation modality, make consensus on operability among surgeons and medical oncologists, and recruit more participating institutions.

Conclusions

The addition of radiotherapy to the induction chemotherapy regimen for stage IIIA (N2) NSCLC appears to confer better local control without adding significant adverse events. The favorable local control in this CRS arm did not translate to a significant survival difference. We consider this was due to the small sample size. Tumor downstaging after induction therapy is an important factor for improving patient survival.

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CONFLICT OF INTEREST DISCLOSURE

The authors made no disclosure.

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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

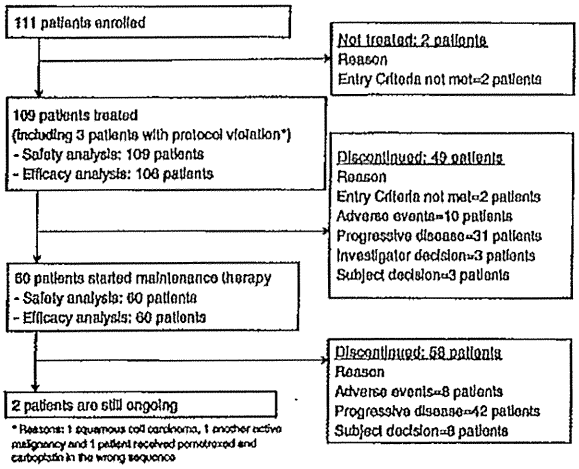

Fig. 1 Patient disposition

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

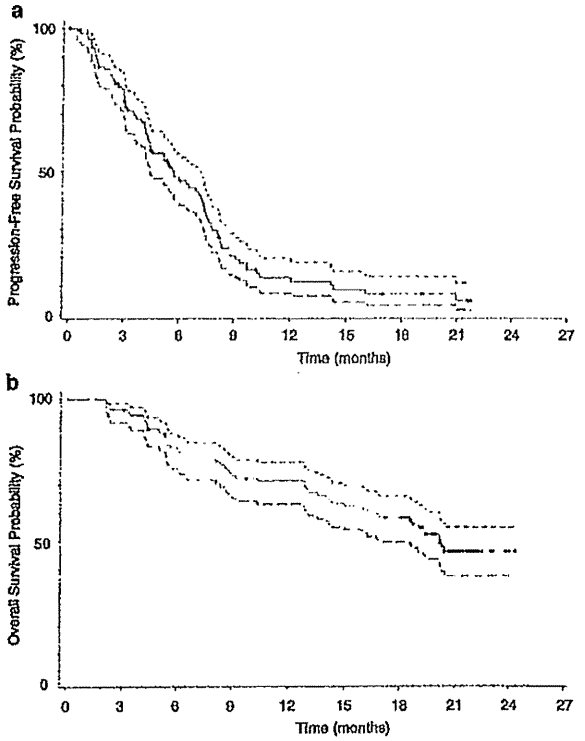

Fig. 2 a. Kaplan-Meier curves for progression-free survival curve (*solid line*) with 95 % confidence band (*dashed lines*). b. Kaplan-Meier curves for overall survival curve (*solid line*) with 95 % confidence band (*dashed lines*)

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

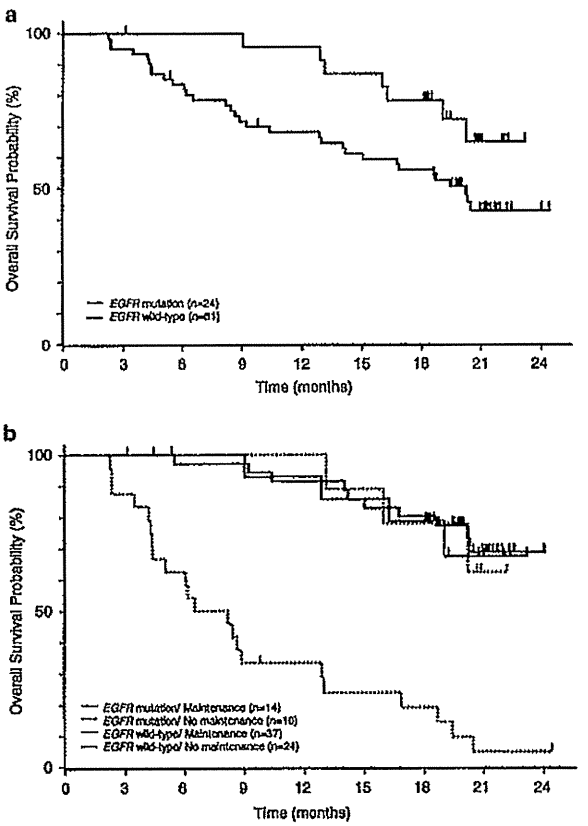

Fig. 3 a. Overall survival by EGFR mutation status. b. Overall survival by EGFR mutation status and maintenance-treated status

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