Phase II study of irinotecan plus S-1 combination for previously untreated advanced non-small cell lung cancer: Hokkaido Lung Cancer Clinical Study Group Trial (HOT) 0601

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ABSTRACT

Objective: Platinum-free regimens can represent an alternative for advanced non-small cell lung cancer (NSCLC) if similar efficacy is provided with better tolerability. This study evaluated the efficacy and safety of combined irinotecan and S-1 for chemotherapy-naïve advanced NSCLC.

Methods: Chemotherapy consisted of 4-week cycles of intravenous irinotecan (100 mg/m^2, days 1 and 15) and oral S-1 (80 mg/m^2, days 1-14). The primary endpoint was response rate, while secondary endpoints were overall survival (OS), progression-free survival (PFS), and safety.

Results: A total of 112 cycles was administered to 40 patients (median, 3 cycles; range, 1-6 cycles). Twelve patients showed partial response (PR) and 17 patients exhibited stable disease (SD), representing a response rate of 30% and a disease control rate of 72.5%. Median survival time and median PFS were 16.1 months and 4.8 months, respectively. Hematological toxicities of grade 3 or 4 were neutropenia (32.5%) and anemia (5.0%). The most common non-hematological toxicities of grade 3 or 4 included diarrhea (15.0%) and anorexia (17.5%). Patients homo- or heterozygous for *UGTA1A*6* tended to show a higher incidence of grade 3 diarrhea (p=0.055).

Conclusion: The combination of irinotecan and S-1 offers good efficacy and tolerability for previously untreated advanced NSCLC.

INTRODUCTION

Platinum-based doublet chemotherapy was established in the 1990s, and it has become the standard first-line therapy for advanced non-small cell lung cancer (NSCLC) [1, 2]. Platinum compounds, particularly cisplatin, are associated with considerable toxicity that may lead to reluctance on the part of both physicians and patients to initiate chemotherapy. Platinum-free regimens can offer a useful substitute if similar efficacy can be provided with reduced toxicity.

Third-generation agents are, in general, better tolerated than their first- and second-generation predecessors, and have shown single-agent activity. The development of new anticancer drugs such as nucleoside analogs, vinca-alkaloids, taxanes, camptothecin-derivatives, and 5-fluorouracil derivatives provide alternatives to these platinum agents [3].

Among the new agents, irinotecan and S-1 have been developed in Japan. Irinotecan, a derivative of camptothecin, inhibits topoisomerase I and shows strong antitumor effects against NSCLC. Fukuoka et al. reported that irinotecan monotherapy showed a 23% response rate (RR) with a median survival time (MST) of 42 weeks for previously untreated NSCLC [4]. In addition, irinotecan plus cisplatin exhibited a RR of 52%, including 1 case of complete response (CR) with an MST of 44 weeks [5].

S-1 is a novel oral fluorouracil antitumor agent that consists of tegafur, 5-chloro-2,4-dihydroxypyridine (gimeracil, which inhibits dihydropyrimidine dehydrogenase) and potassium oxonate (oteracil potassium). In a phase II trial against metastatic NSCLC, S-1 showed a promising RR of 22% with an MST of

10.5 months [6]. S-1 combined with cisplatin or carboplatin exhibited promising efficacy with favorable toxicity profiles [7-11]. In addition, the LETS (Lung Cancer Evaluation of TS-1) study recently demonstrated that S-1 with carboplatin was non-inferior in terms of overall survival (OS) compared with carboplatin and paclitaxel in patients with advanced NSCLC [12].

In preclinical models, optimal therapeutic synergy was observed with irinotecan plus S-1 or 5-fluorouracil combination [13, 14]. The apoptosis rate of colon cancer cells increased after treatment with irinotecan plus 5-fluorouracil, corresponding to activation of Bax [13]. A potential mechanism of synergy between irinotecan plus S-1 was also suggested by the significant reduction in levels of thymidylate synthase [14].

Several studies of combination therapy with irinotecan plus S-1 have shown promising activity and safety, particularly for gastric or colorectal cancer [15, 16]. These findings led us to investigate the possibility of irinotecan combined with S-1 as a first-line regimen for NSCLC. This prospective phase II study evaluated the efficacy and safety of irinotecan plus S-1 therapy. As a supplemental study, associations between *UGT1A1* genotypes (**6* and **28*) and frequency of severe toxicity were also examined.

PATIENTS AND METHODS

Patient Eligibility

The ethics review boards at each participating institute approved this study, and each patient provided written informed consent prior to enrollment. Main eligibility criteria were: 1) histologically or cytologically confirmed NSCLC;

2) stage III disease without indication for curative irradiation, stage IV disease, or postoperative recurrence; 3) no prior chemotherapy; 4) measurable or assessable disease; 5) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2; 6) age between 20 and 75 years with white blood cell (WBC) count ≥3,000/mm^3, hemoglobin ≥9.5 g/dl, platelet count ≥100,000/mm^3, total bilirubin ≤1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase less than twice the upper limit of normal, creatinine ≤1.5 mg/dl, P_aO_2 ≥65 Torr or SpO_2 ≥92%; and 7) anticipated survival ≥3 months. Main exclusion criteria were: 1) serious concomitant systemic disorders including severe heart failure, uncontrollable angina, hypertension, diabetes mellitus, interstitial pneumonia, active infection, ulcer, or another primary malignancy; 2) symptomatic brain metastases; 3) history of severe hypersensitivity; and 4) pregnancy.

Treatment Schedule

All patients received irinotecan (100 mg/m^2) on days 1 and 15. S-1 (40 mg for patients with body surface area (BSA) ≤1.25 m^2; 50 mg for patients with BSA >1.25 m^2 but ≤1.5 m^2; and 60 mg for patients with BSA ≥1.5 m^2) was administered twice daily for 2 weeks (days 1-14) followed by a 2-week pause. The treatment cycle was repeated every 4 weeks, and all patients received at least 4 cycles unless disease progressed, unacceptable toxicity occurred, the patient refused further treatment, or the physician decided to discontinue treatment. Second-line chemotherapy or other subsequent treatments were initiated at the discretion of the physician according to the protocol.

During the cycle, irinotecan was administered on day 15 when the patient met the following criteria: leukocyte count ≥2,000/mm^3; neutrophil count ≥1,000/mm^3; platelet count ≥50,000/mm^3; total bilirubin ≤1.5 mg/dl; no diarrhea or infection ≥grade 2; and no non-hematological toxicities ≥grade 3. S-1 was stopped for: leukocyte count <2,000/mm^3; neutrophil count <1,000/mm^3; platelet count <50,000/mm^3; total bilirubin ≥1.5 mg/dl; infection or diarrhea ≥grade 2; or non-hematological toxicities ≥grade 3.

Subsequent cycles were delayed until recovery for: leukocyte count <3,000/mm^3; neutrophil count <1,500/mm^3; platelet count <100,000/mm^3; total bilirubin ≥1.5 mg/dl; any infection or diarrhea; PS worsened to ≥PS 3; or any non-hematological toxicities ≥grade 3.

Dose reductions of both agents were made in subsequent cycles for: grade 4 neutropenia lasting ≥4 days; febrile neutropenia; thrombocytopenia <20,000/mm^3; or non-hematological toxic effects ≥grade 3 except for anorexia, nausea, and vomiting. The dose of either S-1 or irinotecan alone was reduced for the next course when S-1 was stopped longer than 4 days or irinotecan had not been administered on day 15 in the previous cycle. When the patient experienced adverse events even after the first reduction, no second reduction was permitted and the protocol treatment was terminated.

Treatment Assessment

Physical examination, electrocardiography, determination of PS, laboratory tests, and chest radiography were performed at baseline and repeated at least every 2 weeks during treatment. Tumor responses were

assessed using chest radiography, computed tomography (CT), or magnetic resonance imaging (MRI) (when clinically indicated) before and during treatment and repeated at least every month until progression. Responses were classified as CR, partial response (PR), stable disease (SD), progressive disease (PD) or non-evaluable (NE) on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 [17]. Disease control rate (DCR) was defined as the sum of the objective response (CR or PR) rate plus the rate of SD. Progression was defined as progressive disease according to RECIST 1.0, clinical progression as judged by the investigator, or death from any cause without progression. Clinical response data were all confirmed by a central review.

Progression-free survival (PFS) was counted from the date of enrollment to the date on which progressive disease was first confirmed by the assessment of the investigator. OS was calculated from the date of enrollment to the date of death or confirmation of survival. For patients without any events, data were censored on the last date with non-event status. The National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0 were used to grade adverse events.

Study Endpoints and Statistical Considerations

The primary endpoint was overall response rate (ORR). Sample size was calculated as 36 in total to confirm an RR of 40% as a desirable target level and RR of 20% as uninteresting with an alpha error of 0.05 and a power of 0.8. Allowing for a patient ineligibility rate of 10%, we initially planned to enroll 40 patients. Secondary endpoints were PFS, OS, and toxicity profiles. Survival

outcomes were estimated using the Kaplan-Meier method.

UGT1A1 Analyses

All *UGT1A1* analyses were performed at Bio Medical Laboratories (Tokyo, Japan) using the Invader assay. Briefly, DNA was extracted from peripheral blood samples according to instructions from the manufacturer. The Invader assay detects *UGT1A1* genotypes by use of cleavase enzyme and a fluorescence resonance energy transfer cassette. Probes were designed for detecting the genotypes associated with *UGT1A1**6 and *28. The *UGT1A1**6 target site is 211G/A in exon 1, and *UGT1A1**28 has 7 TA repeats within the TATA box, as previously reported [18, 19].

RESULTS

Patient Characteristics

Forty patients (28 men, 12 women) from 8 institutions were enrolled in this study from August 2006 to July 2008. Patient characteristics are outlined in Table 1. Median age at the time of entry to the study was 64 years (range, 42-75 years). ECOG PS was 0 in 23 patients (57.5%), and 32 patients (80%) had stage IV disease. In addition, 29 (72.5%) patients had adenocarcinoma, and 8 (20%) had squamous cell carcinoma.

Response to Therapy and Survival

The 40 patients received a total of 112 cycles (median, 3 cycles; range, 1-6 cycles), with 19 patients (47.5%) completing ≥4 cycles. The dose of agents

was reduced in 14 patients (35%) because of toxicities, and protocol treatment was terminated in 21 patients (52.5%) before completion of 4 cycles. Of the 21 patients, treatment was discontinued in 9 patients because of disease progression and in 12 patients who experienced unacceptable toxicity (Table 2). Mean relative dose intensities of S-1 and irinotecan were 95% each. Subsequently, 38 patents were assessable for tumor responses. Twelve patients exhibited PR, and 17 patients exhibited SD, resulting in a RR of 30% (95% confidence interval (CI), 16.6-46.5%) and a disease control rate of 72.5% (95%CI, 56.1-85.4; Table 3). The lower end of the 95%CI was thus lower than the threshold ORR of 20%, and the primary endpoint was not met. Disease progressed in 9 cases. The final survival assessment was carried out in March 2010 (>1 year after the last patient enrollment). With a median follow-up time of 16.1 months, MST and median PFS for all enrolled patients were 16.1 months (95%CI, 10.3-22.0 months) and 4.8 months (95%CI, 3.8-6.3 months), respectively (Figs. 1, 2). One-year survival rate was 60.0% (95%CI, 43.3-75.1%).

We then conducted post-hoc analysis to evaluate differences in efficacy outcomes between histological types. ORRs were 34.5% (95%CI, 17.9-54.3) in adenocarcinoma (n=29) and 12.5% (95%CI, 0.3-52.7) in squamous cell carcinoma (n=8). In addition, the adenocarcinoma group showed an MST of 17.2 months (95%CI, 13.7-22.7 months), whereas the squamous cell carcinoma group had an MST of 9.3 months (95%CI, could not be determined). The Kaplan-Meier plot of overall survival by histological type is shown in Figure 3.

Toxicity profiles

Severe adverse events were uncommon and were manageable in most cases. Overall, the most common hematological adverse events were leukopenia (60.0%), neutropenia (55.0%), anemia (70.0%), and thrombocytopenia (20.0%), while the most common non-hematological adverse events were diarrhea (62.5%), nausea (50.0%), and anorexia (62.5%). Stomatitis was of grade 1 to grade 2 in severity (grade 1, 3 cases; grade 2, 1 case). Hematological toxicities of grade 3 or 4 included leukopenia (10.0%), neutropenia (32.5%) and anemia (5.0%). The most common non-hematological toxicities of grade 3 or 4 included diarrhea (15.0%), nausea (7.5%), and anorexia (17.5%) (Table 4). Grade 2 interstitial lung disease was reported in 1 patient, resolving after termination of the protocol treatment. Subsequently, no treatment-related deaths were encountered.

Treatment after protocol discontinuation

Although any treatment was permitted, the majority of enrolled patients received platinum-based regimen as a second-line treatment. Twenty-two patients (55.0%) received carboplatin plus paclitaxel, and 3 patients (7.5%) received carboplatin plus docetaxel. Four patients (10.0%) showed sensitive *EGFR* mutation, and all four received second-line gefitinib monotherapy, resulting in SD response.

UGT1A1 Genotype Analysis and Associations with Toxicity

The 40 patients included 1 patient homozygous and 8 patients heterozygous for *UGT1A1*6,* compared to 7 patients heterozygous for *UGT1A1*28*. No patients showed both genotypes. Patients who were homo- or heterozygous for *UGTA1A*6* showed a trend toward high incidence of grade 3 diarrhea (p=0.055). No relationship was identified between grade 3 or 4 neutropenia and *UGT1A1*6* (p=0.32). The patient harboring homozygous *UGTA1A*6* showed grade 3 neutropenia and diarrhea. No association of *UGT1A1*28* with severe toxicity was observed. The grade 2 interstitial lung disease developed in a patient heterozygous for *UGT1A1*28.*

DISCUSSION

There is an obvious need for equally active but better-tolerated regimens to optimize therapy for advanced NSCLC. This phase II trial employing irinotecan plus S-1 as a first-line therapy for chemotherapy-naïve NSCLC revealed a promising RR of 30% and an MST of 16.1 months, although the primary endpoint of ORR was not met. Furthermore, toxicity was manageable overall, with low frequencies of grade 3 or 4 hematological and non-hematological toxicities including neutropenia, diarrhea, nausea, and anorexia. Collectively, the present study demonstrated irinotecan plus S-1 as a promising and well-tolerated regimen for first-line treatment of advanced NSCLC.

Of note was the finding that utilizing combination therapy, RR and MST were significantly inefficacious against squamous cell carcinoma compared to

adenocarcinoma. A previous study found no significant difference in PFS or RR with cisplatin plus S-1 by histological type [20]. Irinotecan plus S-1 has been developed for gastrointestinal malignancies. A limited number of squamous cell carcinomas were treated in this study. So whether irinotecan plus S-1 is effective against non-adenocarcinoma histologies should be further evaluated.

Several randomized phase II trials have compared cisplatin-based therapy with cisplatin-free therapy in the first-line treatment setting. Docetaxel/gemcitabine and vinorelbine/cisplatin combinations showed similar efficacy (RR, 30.0% vs. 39.2%, respectively) and survival data (MST, 9.0 months vs. 9.7 months, respectively), while the cisplatin-free regimen showed less toxicity [21]. Gemcitabine plus vinorelbine was also compared with cisplatin plus vinorelbine or cisplatin plus gemcitabine [22]. No significant differences in the primary endpoint of quality of life were seen between the platinum and non-platinum arms, with comparable MSTs of 38 and 32 weeks, respectively. Subsequent meta-analysis showed that non-platinum third-generation-based combination regimens offer comparable efficacy with less toxic profiles when compared with platinum-based regimens [23]. Our findings likewise showed that the efficacy of combined irinotecan and S-1 is equivalent to that of the reported platinum doublet regimens, although limitations exist in comparing results between different studies.

Two clinical trials using the S-1 and irinotecan combination for untreated NSCLC have recently been reported from Japan. In a phase I trial, patients with advanced NSCLC received S-1 (80 mg/m^2) on days 1-14 and irinotecan (50-80 mg/m^2) on days 1, 8, and 15 of each 28-day cycle. That study concluded by

recommending 70 mg/m^2 as the weekly dose of irinotecan [24]. In the WJTOG 3505 phase II study, patients were treated with irinotecan at 150 mg/m^2 on day 1 and oral S-1 at 80 mg/m^2 on days 1-14 every 3 weeks. That study showed an ORR of 28.6%. Median PFS was 4.9 months, whereas median OS was 15 months, with favorable toxicity profiles [25]. Other non-platinum regimens utilizing S-1 have also been reported, such as docetaxel plus S-1 or gemcitabine plus S-1 [26-29]. Efficacies were almost the same, although higher rates of myelosuppression with ≥ grade 3 neutropenia were observed, particularly in the docetaxel plus S-1 arm.

A phase II trial of irinotecan and S-1 for advanced gastric cancer using the same treatment schedule as in the present study revealed good efficacy (RR, 54.2%) and dose intensity [16], which encouraged us to apply that schedule in the present study for NSCLC. Dose intensity in our study was 95% for S-1 and 95% for irinotecan, in line with the findings of the WJTOG 3505 study. Recently, the FIRIS study reported that PFS with irinotecan plus S-1 (IRIS) was non-inferior to that with FOLFIRI (fluorouracil and folinic acid plus irinotecan) in a second-line treatment setting for metastatic colorectal cancer [30]. In that study, irinotecan was also administered on days 1 and 15 for the IRIS regimen. The best treatment schedule of irinotecan plus S-1 for lung cancer has yet to be determined, warranting further studies.

Determination of *UGT1A1* genotypes might be clinically useful for predicting severe toxicity by irinotecan. The presence of the *UGT1A1**6 allele was associated with severe grade 4 neutropenia compared with patients showing the reference genotype [18]. Genotypes either hetero- or homozygous

for *UGT1A1**28 represent a significant risk factor for severe toxicity from irinotecan [19]. In this study, no association between *UGT1A1* genotypes and severe toxicity was observed. As the trial was powered for the primary endpoint, supplemental analyses were based on smaller numbers of patients and statistically meaningful analysis may thus have been precluded. Some prospective trials are underway to clarify whether reducing irinotecan dose is necessary for patients showing *UGT1A1* genotypes.

Various limitations to this study need to be considered. First, the majority of patients in this study had adenocarcinoma (73%). Patient selection could thus have contributed to survival outcomes. Second, EGFR mutation testing was performed for 17 patients, accounting for 42.5% of enrolled patients. We were therefore unable to assess the effects of EGFR mutation on overall survival. Finally, the study population was entirely Japanese, and the efficacy of this combination therapy thus may not be valid among non-Asian NSCLC patients.

In conclusion, the regimen of irinotecan and S-1 conferred similar survival benefits with good tolerability when compared with previously reported platinum-based regimens. This combination might represent an alternative to first-line chemotherapies for advanced NSCLC, and a more extensive clinical trial is warranted to verify the efficacy of this regimen.

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FIGURE LEGENDS

Figure 1. Overall survival, median 16.1 months (95%CI, 10.3-22.0 months)

Figure 2. Progression-free survival, median 4.8 months (95%CI, 3.8-6.3 months)

Figure 3. Overall survival by histological type, median 17.2 months (95%CI, 13.7-22.7 months) for adenocarcinoma and 9.3 months (95%CI, could not be determined) for squamous cell carcinoma

Figure 1. Overall Survival

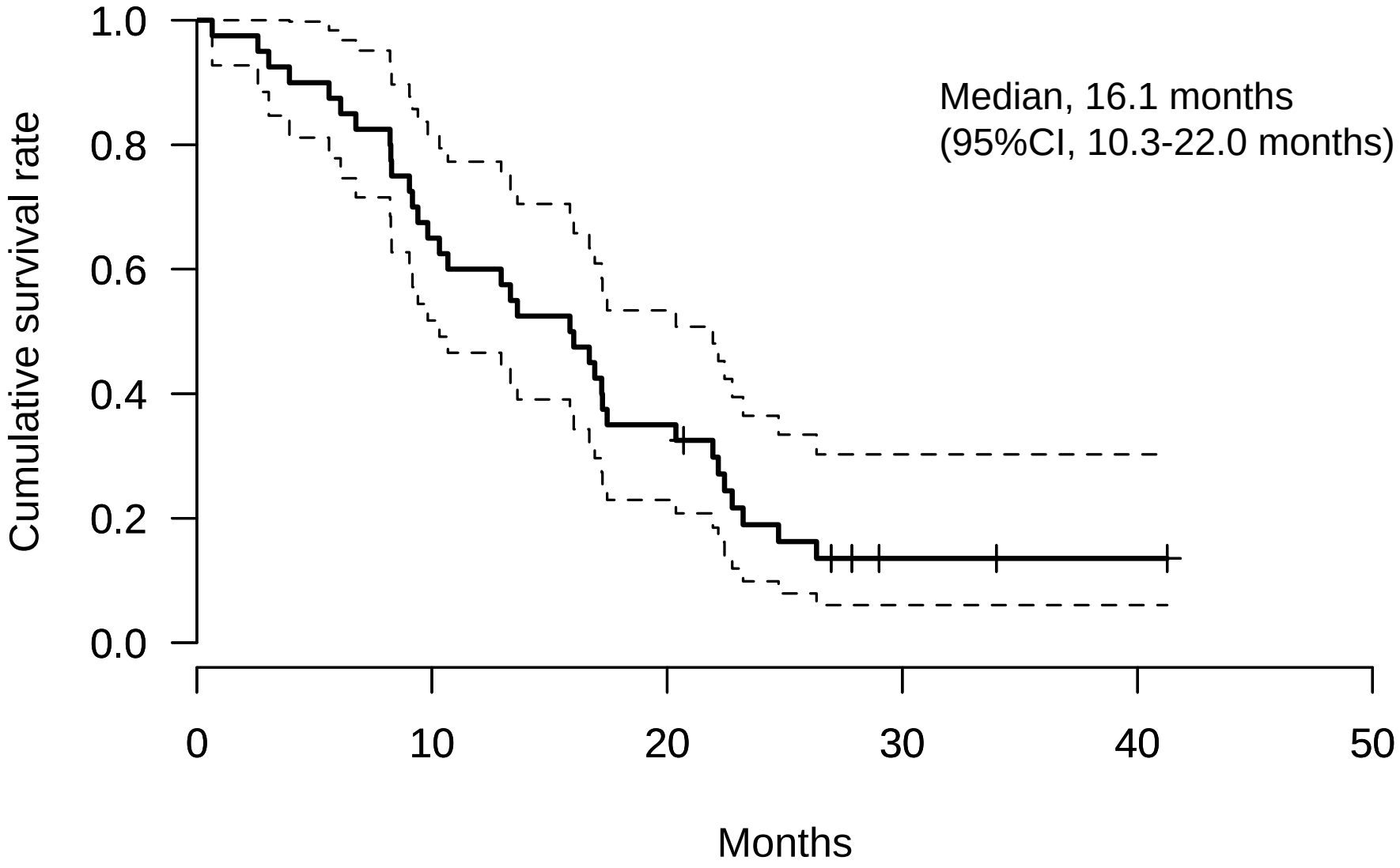

Figure 2. Progression-free Survival

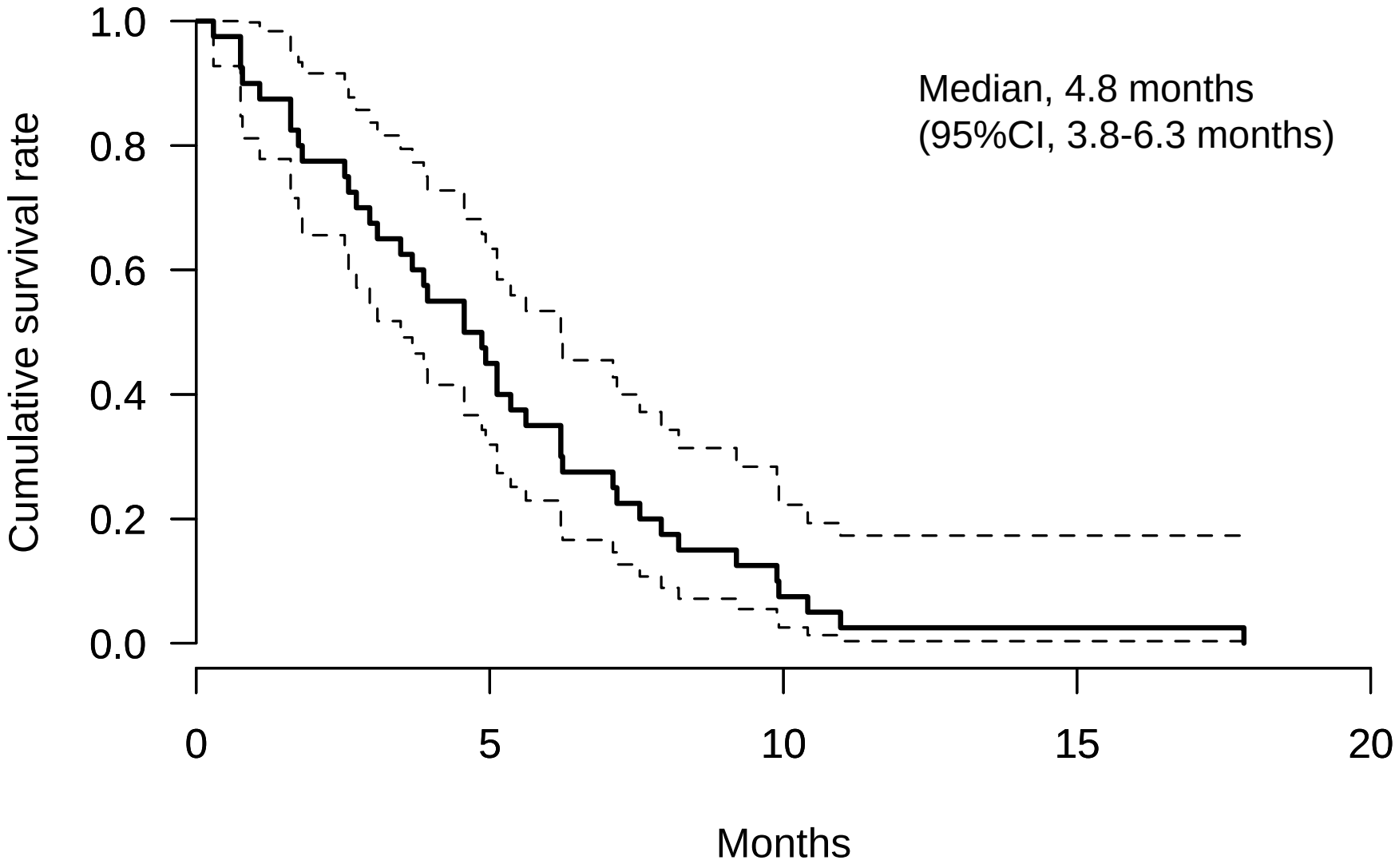

Figure 3. Overall Survival by Histological Type

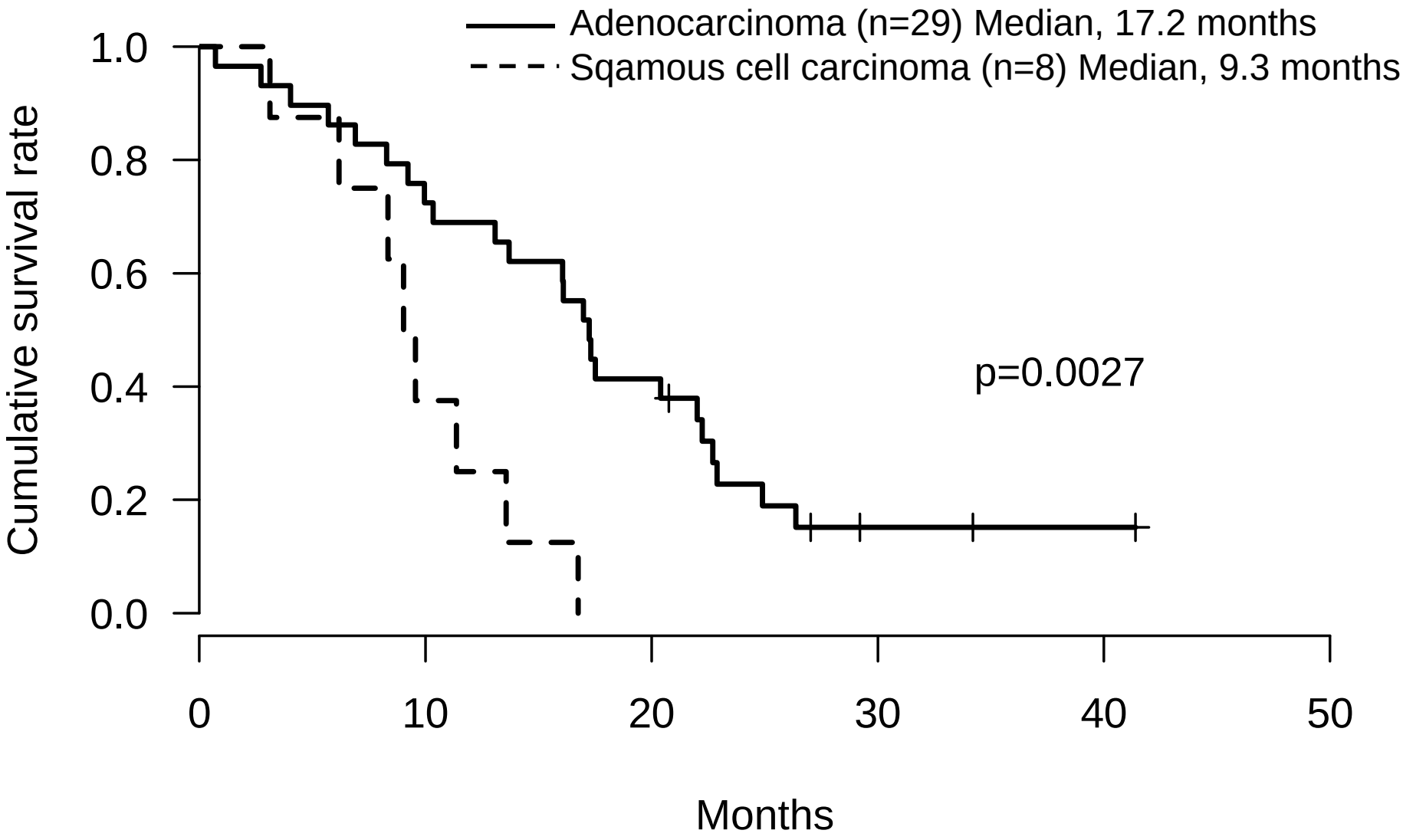

Table 1. Patient characteristics

Characteristic	n	(%)
Age (years)		
Median	64	
Range	42-75	
Sex		
Male	28	70.0
Female	12	30.0
ECOG performance status		
0	23	57.5
1	17	42.5
Disease stage		
IIIB	6	15.0
IV	32	80.0
Recurrence after surgery	2	5.0
Histology		
Adenocarcinoma	29	72.5
Squamous cell carcinoma	8	20.0
Unclassified NSCLC	3	7.5

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small-cell lung cancer.

Table 2. Reason for discontinuation of protocol treatment

	Cycle 1	Cycle 2	Cycle 3	Total
Disease progression	4	3	2	9
Unacceptable toxicity	4	6	2	12

Table 3. Overall response

Response	n (%)
Complete response	0 (0%)
Partial response	12 (30%)
Stable disease	17 (42.5%)
Progressive disease	9 (22.5%)
Not evaluable	2 (5.0%)

Response rate: 30% (95%CI, 16.6-46.5%)

Disease control rate: 72.5% (95%CI, 56.1-85.4%)

Table 4. Toxicity for all cycles

Toxicity	Grade				Grade ≥3 (%)
	1	2	3	4	
Leukopenia	9	11	4	0	10.0
Neutropenia	5	4	12	1	32.5
Anemia	14	12	2	0	5.0
Thrombocytopenia	7	1	0	0	0
Diarrhea	12	7	6	0	15.0
Nausea	10	7	3	0	7.5
Vomiting	2	3	1	0	2.5
Anorexia	13	5	7	0	17.5