A Multi-center Phase II Study of Adjuvant Chemotherapy with Oral Fluoropyrimidine S-1 for Non-Small Cell Lung Cancer: High Completion and Survival Rates

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Conflict of Interest

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MicroAbstract

As oral chemotherapy might reduce physiological and psychological burdens on patients, we conducted a feasibility study using S-1, an oral fluoropyrimidine, as postoperative chemotherapy in 50 patients with curatively resected stage IB-IIIA non-small cell lung cancer. The completion rate was 72.0% and the 3-year relapse-free survival rate was 69.4%. This protocol seems feasible and may be sufficient to prevent recurrence.

Abstract

Background: Oral adjuvant chemotherapy without hospitalisation might reduce the physiological and psychological burden on patients if effectiveness could be guaranteed. We conducted a multi-center feasibility study using S-1, an oral derivative of 5-fluorouracil, as postoperative adjuvant chemotherapy in patients with curatively resected pathologically stage IB-IIIA non-small cell lung cancer. **Patients and Methods:** Adjuvant chemotherapy comprised eight courses (4-week administration, 2-week withdrawal) of S-1 at 80-120 mg/body/day. Fifty-one patients from seven institutions were enrolled in this pilot study, from June 2005 to March 2007. The primary endpoint was the completion rate of scheduled adjuvant chemotherapy. Secondary endpoints were the incidence and grade of adverse reactions. **Results:** Fifty patients were eligible. The completion rate for the planned eight courses of S-1 administration was 72.0% (36 patients). Total percentage administration amount was 71.1%. Grade 3 adverse reactions such as neutropenia (4.0%), anorexia (4.0%), thrombopenia (2.0%), anemia (2.0%), elevated total bilirubin (2.0%), hypokalemia (2.0%), nausea (2.0%) and diarrhoea (2.0%) were observed, but no grade 4 adverse effects were encountered. Overall and relapse-free survival rates at 3 years were 87.7% and 69.4%, respectively. **Conclusion:** Postoperative 1-year administration of S-1 seems feasible as oral adjuvant chemotherapy for lung cancer. The oral formulation and low incidence of adverse reactions permit treatment on an outpatient basis. The present study would be reasonable to follow up with a properly powered phase III trial.

Keywords: Non-small cell lung cancer, Adjuvant chemotherapy, Fluoropyrimidine, S-1, Feasibility study

Introduction

The results of surgical treatment for lung cancer have been improved by early detection and meticulous surgical procedures. However, we still face recurrence in patients with advanced lung cancer, even after extended surgical treatment. Since 2004, clinical research studies have established the efficacy of adjuvant chemotherapy in post-operative patients with stage IB-IIIA non-small cell lung cancer (NSCLC).[1-3] Standard regimens for adjuvant chemotherapy currently use intravenous administration of a platinum doublet. However, oral adjuvant chemotherapy with uracil-tegafur, which improved survival among patients with completely resected stage IB adenocarcinoma, allows completion of the regimen with only mild adverse reactions.[1] Such oral drugs enable patients to undergo treatment on an outpatient basis, and are suitable for maintaining patient quality of life.

S-1 is a novel oral fluoropyrimidine derivative consisting of tegafur (FT) and two modulators, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo), in a molar ratio of 1:0.4:1.[4] FT is a prodrug of 5-fluorouracil (5-FU) and CDHP is a reversible competitive inhibitor of dihydropyrimidine dehydrogenase (DPD; EC1.3.1.2), an enzyme involved in the degradation of 5-FU. Degradation of FT-derived 5-FU is thus efficiently inhibited by CDHP, and 5-FU remains in plasma and tumor tissue longer and at higher levels than when low-dose 5-FU is continuously infused intravenously. The major toxicities associated with fluoropyrimidines are diarrhoea and mucositis.[5] Oxo is a reversible competitive inhibitor of orotate phosphoribosyltransferase (EC2.4.2.10), a phosphoenzyme for 5-FU, and is distributed at high levels in the gastrointestinal (GI) tract after oral administration, reducing GI toxicity caused by 5-FU.[6]

Response rates for platinum doublet therapy in patients with advanced lung cancer are 30-33%.[7] Conversely, S-1 showed a 22% response rate for advanced NSCLC in a previous phase II trial,[8] raising the question of whether S-1 has sufficient power as adjuvant

chemotherapy. In that regard, the therapeutic strategy with oral fluoropyrimidine differs from that with intensive platinum doublets. Despite showing a response rate of only 7% for advanced NSCLC, uracil-tegafur, another oral fluoropyrimidine, could be administered long-term (2 years) and, thus, could allow administration of sufficient amounts to prevent recurrence or metastasis, because the drug has extremely low toxicity and is easily continued as an oral medication.[9] Although the exact mechanisms of action accounting for the efficacy of uracil-tegafur treatment in the postoperative adjuvant setting remain unclear, long-term uracil-tegafur administration may inhibit the development of postoperative recurrence through antiangiogenic effects in addition to direct cytotoxic effects.[10] In terms of S-1-based adjuvant chemotherapy, in the field of gastric cancer, a feasibility study has already been performed and achieved a high completion rate of 60% and a favorable drug compliance rate of 70%.[11] Furthermore, a phase III randomized study comparing surgery alone to surgery plus adjuvant chemotherapy using S-1 was ongoing in 2005.[12] Given this background, we presumed that if long-term administration could be achieved in the postoperative adjuvant setting, similar factors would be applicable even for stage II to IIIA disease because of the higher response rate compared to uracil-tegafur.

Based on similar notions, a feasibility study for adjuvant chemotherapy was reported by Yano *et al.* in 2010.[13] In that study, 56.7% of patients finished the regimen. Postoperative administration of S-1 for 6 months was thus considered feasible as adjuvant chemotherapy for NSCLC. However, the administration period of 6 months is half the reported duration of the adjuvant chemotherapy with S-1[12] and the completion rate is unsatisfactorily low despite the mildness of adverse reactions. Moreover, survival data from the study have yet to be reported.

To confirm the feasibility of 1-year administration of S-1 and analyse the effect of the intervention on prognoses, a multi-center phase II clinical trial was conducted in seven facilities.

Patients and Methods

Patient Eligibility

Patient eligibility required compliance with the following criteria: NSCLC with histological proof; pathological stage IB, II, or IIIA NSCLC (according to the fifth edition of UICC/AJCC 1997)[14] after complete resection; no prior treatment except for surgery; age >20 and <80 years, with sufficient oral intake; and performance status (PS) 0 or 1. Patients also had to have adequate organ function ($3500 \leq$ leukocytes $\leq 12{,}000/mm^3$; thrombocytes, $\geq 100{,}000/mm^3$; total bilirubin, $\leq$1.5 mg/dl; aspartate aminotransferase and alanine aminotransferase, less than twice the normal limits at each institution; blood urea nitrogen, $\leq$25 mg/dl; creatinine, less than the normal limits at each institution; and creatinine clearance (Ccr) as estimated by the Cockcroft-Gault formula, $\geq$50 ml/min). Patients with a history of drug hypersensitivity, serious surgical or non-surgical complications, or active secondary cancer were excluded. Pregnant or lactating women were likewise excluded.

Treatment Schedule

Chemotherapy comprised eight courses (4-week administration, 2-week withdrawal) of S-1 (FT, gineracil, oteracil potassium; Taiho Pharmaceutical, Tokyo, Japan) at 80-120 mg/body/day according to body surface area (BSA): BSA <1.25 m^2, 80 mg/day; BSA $\geq$1.25 m^2 but <1.5 m^2, 100 mg/day; and BSA $\geq$1.5 m^2, 120 mg/day. S-1 was administered orally, twice daily after meals, starting within 4 weeks after surgery. Every 6 weeks, patients visited the hospital and drug compliance was checked from the treatment diary. Subjective

symptoms, clinical experiment including hematological toxicities and tumor markers were also confirmed. The administration dose for the next course was determined after checking these data. Doses were modified in accordance with the following guidelines. When adverse reactions appeared, the dose was reduced from 120 to 100 mg/day or from 100 to 80 mg/day, or administration was temporarily discontinued. Restarting was approved when adequate organ function was recovered and fulfilled the following criteria: leukocytes, $\geq$3,000/mm^3; neutrophils, $\geq$1,500/mm^3; thrombocytes, $\geq$100,000/mm^3; total bilirubin, $\leq$1.5 mg/dl; aspartate aminotransferase and alanine aminotransferase, less than twice the upper limits of normal at each institution; blood urea nitrogen, $\leq$25 mg/dl; creatinine, less than the upper limit of normal at each institution; and creatinine clearance (Ccr) as estimated by the Cockcroft-Gault formula, $\geq$50 ml/min. When treatment was restarted within 14 days, the restart was judged to represent the same course after temporary discontinuation of drug administration. When treatment could not be restarted within 14 days, the course was skipped and restarted as the next course. Treatment was discontinued when the patient showed disease recurrence or adverse reactions that were uncontrollable by dose modification and temporary discontinuation of drug administration. If a rest period >4 weeks was required, the patient was withdrawn from the study. National Cancer Institute Common Toxicity Criteria (NCI-CTC, 1998) were adopted for the evaluation of chemotherapy toxicity.

Study Design and Statistical Analysis

This trial was non-blinded and open-label. The primary endpoint was the completion rate of the scheduled adjuvant chemotherapy. Secondary endpoints were the incidence and grade of adverse reactions. The number of patients to be enrolled in this study was calculated as 55. Assuming a completion rate of 70%, with a planned eligible sample size of 50 patients, the 95% confidence interval (CI) for the completion rate was estimated to range from 55% to

82%. This completion rate of 70% means that 70% of patients would complete 48 weeks of planned chemotherapy.

The Kaplan-Meier method was used to estimate the time-to-event functions of relapse-free survival and overall survival. Relapse-free survival has been defined as the time from the date of the start of treatment to the date of disease progression or death (whichever occurs first) or the date of last contact. Overall survival has been defined as the time from the date of the start of treatment to the date of death or last contact. The log-rank test was used to test for possible differences between estimated time-to-event curves.

Ethics

This study was approved by the institutional review board at each site. Patients selected whether they would participate in the trial or not after detailed explanation and written informed consent was obtained from all patients prior to enrolment. In terms of one institution (Nagasaki University Hospital), 52 patients were referred to the trial. Among the referred patients, 15 patients participated in the trial, 14 patients preferred to received uracil-tegafur (p-stage IB), and 23 patients preferred to received standard chemotherapy.

Results

Patient Characteristics

A total of 51 patients were initially enrolled in the present study. One patients were ineligible, who rescinded consent to enter the trial before administration of S-1. Table 1 shows the characteristics of the 50 eligible patients. The median age of patients was 71.0 years (range, 32-80 years). Lobectomy was performed in all patients.

Drug Compliance

Table 2 shows drug compliance in each course and reasons for discontinuation of drug administration. The planned eight courses of S-1 were administered to 36 patients (72.0%). Among these 36 patients, 25 patients received dose reduction (69.4% of 36 patients). Thirteen patients discontinued drug administration because of anorexia, diarrhoea, thrombocytopenia, elevated total bilirubin, fever, or stomatitis (n=5). Non-iatrogenic reasons for discontinuation included patient refusal (n=6), transfer to a different hospital (n=1) and administrative errors (n=1). The discontinued case occurred within the third course and drug compliance was maintained at >85% (85.4-99.4%) in every course. In the total group of 50 patients, the percentage of actual days on which S-1 was administered against the total number of planned administration days (28 days ×8, i.e., 224 days) was 77.3%. Concerning the amount of drug administered, the compliance rate was 71.1%.

Adverse Reactions and Dose Reduction

Table 3 shows a summary of the adverse reactions encountered. Among the laboratory findings-based adverse reactions, increased serum total bilirubin was the most frequent, occurring in 8 of the 50 patients (16.0%), followed by thorombocytopenia (12.0%), anemia (12.0%), and leukocytopenia (10.0%). Among the clinical findings-based adverse reactions, anorexia was the most frequent (42.0%), followed by nausea (12.0%), diarrhoea (6.0%), pigmentation changes (6.0%), stomatitis (4.0%), malaise (4.0%), and constipation (4.0%). Concerning the incidence and grade of laboratory findings-based adverse reactions, grade 3 adverse reactions were seen with neutropenia, thorombocytopenia, anemia, increased serum total bilirubin, and hypokalemia. No grade 4 adverse reactions were identified. In clinical findings-based adverse reactions, grade 3 adverse reactions were observed with anorexia, nausea, and diarrhoea. Again, no grade 4 adverse reactions were encountered.

The completion rate was 86.7% among cases without adverse reactions (Table 4). When adverse reactions occurred, completion rate decreased to 65.7%. However, dose reduction clearly increased the completion rate (79.2%). When administration was restarted without a dose reduction, the completion rate was significantly lower (36.4%).

Survival

Among the 50 patients followed for survival information, only 13 had died and 37 were still alive at the time of analysis. Median follow-up time was 49.0 months (range, 7.3-66.4 months). At the time of analysis, overall survival rate at 36 months was 87.7% (95%CI, 75.2-94.4) (Figure 1). Of the 13 patients who died, 8 had experienced a documented relapse before death. Four patients died of brain infarction, pneumonia, newly developed malignant lymphoma, or interstitial pneumonia 9 months after the discontinuation of S-1 administration. A total of 14 patients relapsed, and the relapse-free survival rate at 36 months was 69.4% (95%CI, 55.2-80.6) (Figure 1). Among the patients who experienced relapse, 6 patients experienced intrathoracic relapse, including five with regional lymphatic metastasis and one with dissemination, and 8 patients showed distant relapse alone.

Discussion

The present study was undertaken to confirm the feasibility of 1-year oral adjuvant chemotherapy with S-1 after standard resection for NSCLC. The completion rate for the planned eight courses of S-1 administration was 72.0%, which compares favourably to the chemotherapy compliance seen on trials of cisplatin-based adjuvant therapies that have ranged from 45% to 76% of the intended dose.[11-13] Toxicity in the present study was significantly less compared with the other regimen. No grade 4 adverse reactions were observed throughout the eight courses. Only six grade 3 hematological and four grade 3

non-hematological adverse events were encountered (20.0% of total). The most common adverse reaction was grade 1 anorexia, in 42.0% of patients, and administration for outpatients was easily continued. Compared to postoperative adjuvant chemotherapy study using uracil-tegafur, another oral fluoropyrimidine, the frequency of grade 3 adverse reactions was less than 4%. The most common adverse reaction was grade 1 gastrointestinal toxicity, including anorexia, nausea and vomiting in around 10% of patients, representing an extremely low frequency.[1] Conversely, studies of platinum-based postoperative adjuvant chemotherapy have indicated that the frequency of grade 3 or more adverse reactions was more than 69% even with carboplatin-based therapies.[16,18] Accordingly, S-1 is considered to cause intermediate adverse reactions, allowing acceptable compliance. Furthermore, the possibility of outpatient treatment with S-1 is convenient for both doctors and patients.

In the present study, the total percentage administration days and percentage administration dose were 77.3% and 71.1%. Whether a dose reduction of 70% allows sufficient power to prevent recurrence of lung cancer remains unclear. In analysis of a phase III study of postoperative gastric cancer,[12] when protocol completion cases were divided into two groups according to compliance with S-1 administration, the 5-year survival curves for patients with ≥90% compliance and patients with 70% to <90% compliance overlapped (in-house experimental data; Taiho Pharmaceutical). We therefore believe a dose reduction of 70% provides sufficient adjuvant chemotherapy for lung cancer with S-1, as in gastric cancer. Further studies and long-term observations are necessary to clarify the remaining issues.

The regimen in the present study was based on the seminal phase III randomized study in postoperative gastric cancer.[12] Among the 517 patients in the safety population who received S-1, treatment was continued for 12 months in 340 patients (65.8%). In the present study, completion rates were 8% or more higher than those from the study in gastric cancer. In addition, our results showed incidences of hematological and non-hematological adverse

reactions were both lower than in the gastric cancer study. As patients in the gastric cancer study displayed rather advanced disease and received D2 or more aggressive gastrectomy with frequent combined organ resections, patients who undergo standard resection for lung cancer might show better general and intestinal conditions for oral chemotherapy.

In a recent feasibility study of adjuvant chemotherapy with S-1 for NSCLC,[13] the administration period of 6 months and the cycle of 2-week administration and 1-week withdrawal differed from the protocol applied in our study. That study demonstrated no hematological or non-hematological grade 4 adverse reactions throughout the eight courses, very similar to our study. Conversely, completion rate of the planned eight courses of S-1 administration was 56.7%. The reason for the relatively low completion rate was attributed to the high age of patients and the high incidence of patients declining to continue treatment.[13] In the present study, dose reductions were performed without hesitation. When adverse reactions were encountered, dose reduction obviously improved the completion rate to 79.2%, compared to 36.4% without dose reduction. As a result, we achieved a high completion rate of 72.0%. The duration of S-1 administration is another area of discrepancy. Administration of 5-FU is known to be more effective in producing direct cytotoxic effects against human tumor cells using lower doses for longer time periods than using higher doses for shorter times.[19] Our opinion is that at least a year of S-1 is warranted, unless clinical evidence to the contrary is identified.

The overall survival rate among patients with stage IB resected NSCLC was similar to that among patients with stage IIA or more resected NSCLC (data not shown). These data indicate that oral S-1 treatment might have sufficient power to improve survival even in postoperative patients with severe stage NSCLC. Further follow-up survival data are needed for the present study. In addition, randomized phase II and III clinical trials of adjuvant chemotherapy containing S-1 for NSCLCs (WJOG4107 and JCOG0707) are ongoing. The

JCOG0707 phase III study is comparing survival data and compliance between uracil-tegafur and S-1 for stage IA (>2 cm) and IB postoperative patients. The results will provide more reliable data on whether S-1 alone is worthwhile as an option for adjuvant chemotherapy.

One limitation of the present study was the difficulty in confirming true drug compliance. We checked drug compliance from the treatment diary every 6 weeks when the patient visited the hospital, but had no way of ensuring that the patient had made true declarations regarding drug intake. Although most seminal studies have not mentioned this point and one study applied a similar method,[1] investigators must keep in mind that all such oral administration studies conducted on an outpatient basis carry this problem in confirming true drug compliance.

Although S-1 is not well known in Western countries, various clinical trials of S-1-based chemotherapy have been performed or are ongoing for advanced NSCLC, particularly in Japan.[20] Among chemotherapy-naïve patients with advanced NSCLC, a phase III trial by the West Japan Oncology Group showed oral S-1 plus carboplatin was non-inferior in terms of overall survival when compared to paclitaxel plus carboplatin.[21] Comparisons of 5-FU-related enzymes of NSCLC in such patients have indicated that low expression of thymidylate synthase (TS) and dihydropyrimidine dehydrogenase (DPD) are associated with better survival in S-1 plus CBDCA therapy, but not in PTX and CBDCA therapy.[22] As S-1 is a prodrug of 5-FU, we believe the expression of TS, a 5-FU-targeting enzyme, and DPD, a 5-FU-degrading enzyme, are important in determining susceptibility to S-1. Further study of rational differences in 5-FU-related enzymes might be necessary, as expressions of TS and DPD might differ in NSCLC between Western and Eastern populations.

Conclusion

Postoperative 1-year oral administration of S-1 seems feasible as an adjuvant chemotherapy for lung cancer. A high completion rate was achieved when administration doses were decreased by one rank when adverse events were encountered. The oral formulation and low incidence of adverse reactions permit treatment on an outpatient basis. The present findings suggest that follow-up with a properly powered phase III study comparing treatment using S-1 to the standard of care for adjuvant chemotherapy would be reasonable.

Clinical Practice Points

The current standard regimen for adjuvant chemotherapy of NSCLC is intravenous administration of a platinum doublet. However, a seminal study indicated adjuvant chemotherapy with uracil-tegafur, an oral fluoropyrimidine, could improve survival among patients with completely resected stage IB adenocarcinoma. The biggest advantage of such therapy is the low toxicity and easy continuation as oral medication, which can allow long-term administration in amounts sufficient to prevent recurrence. The anti-tumor mechanisms of oral fluoropyrimidine are presumed to differ from those of platinum doublets; long-term administration can inhibit the development of postoperative recurrence through antiangiogenic effects as well as by direct cytotoxic effects.

S-1 is a novel oral fluoropyrimidine derivative consisting of the 5-fluorouracil prodrug tegafur (FT) and two modulators. A modulator of 5-chloro-2,4-dihydroxypyridine (CDHP) is a reversible competitive inhibitor of dihydropyrimidine dehydrogenase (DPD), an enzyme involved in the degradation of 5-FU. As S-1 shows 180-times stronger DPD-inhibiting effect and a higher response rate from patients than uracil-tegafur (22% vs. 7% for advanced NSCLC), we considered this therapy would likely prove beneficial for patients with surgically resected pathological IB to IIIA NSCLC.

The new findings of the present study were that we could achieve a favorable completion rate for 1-year S-1-based adjuvant chemotherapy and also showed the possibility of good prognosis for stage IB to IIIA NSCLC in an adjuvant setting. The clinical impact in the foreseeable future is that the present study confirmed S-1-based adjuvant chemotherapy as worthy of follow-up in a properly powered phase III study comparing with the standard of care for adjuvant chemotherapy.

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Disclosures

All authors report that they have no relevant relationships to disclose.

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Figure Legends

Figure 1 3-year overall survival and relapse-free survival rates

Figure 1

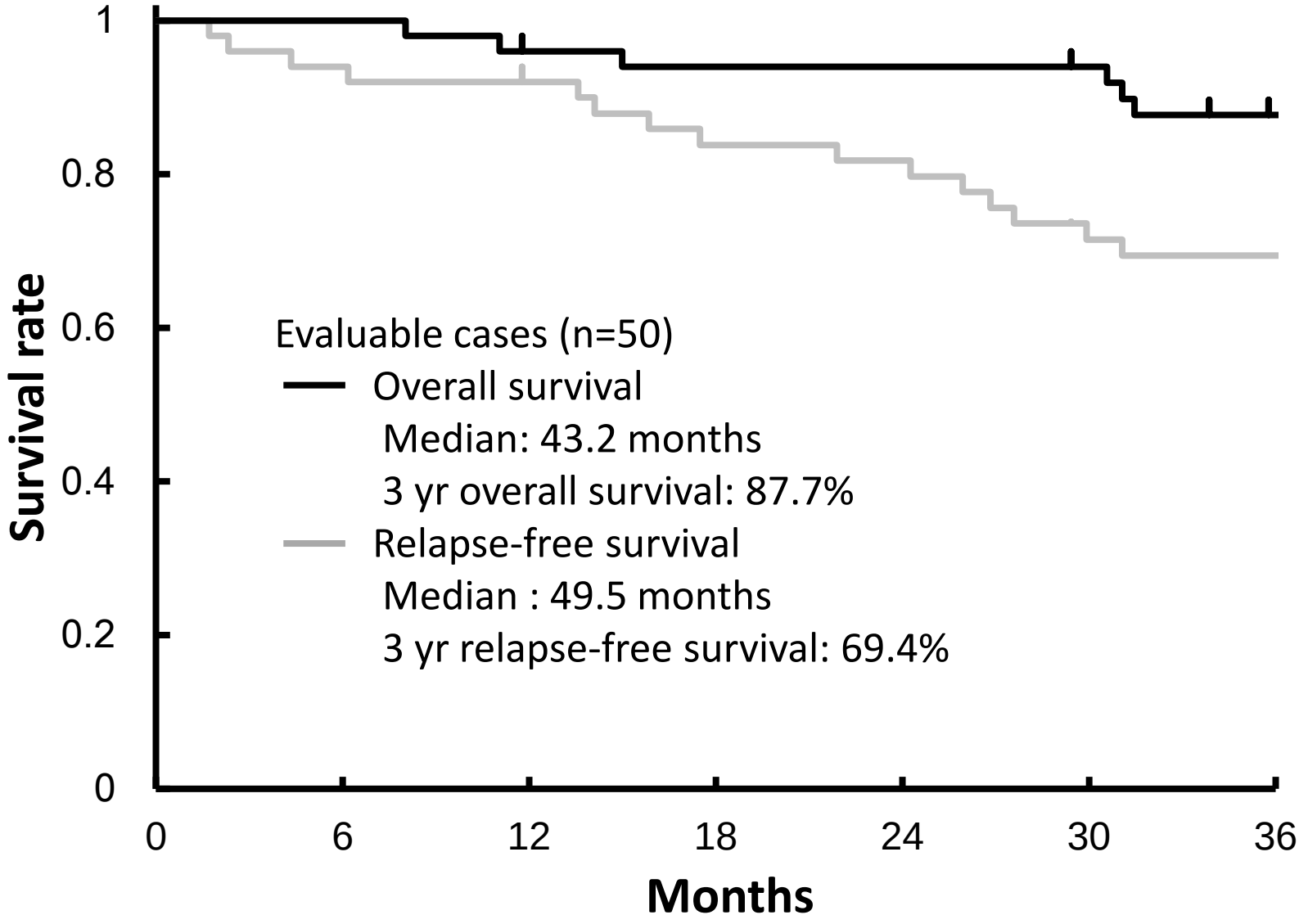
Survival rate
1
0.8
0.6
0.4
0.2
0
0
6
12
18
24
30
36
Months
Evaluable cases (n=50)
Overall survival
Median: 43.2 months
3 yr overall survival: 87.7%
Relapse-free survival
Median : 49.5 months
3 yr relapse-free survival: 69.4%

Table 1 Patient Characteristics (n = 50)

Variables		n	Percentage
Sex	Male	34	68.0
	Female	16	32.0
Age (years)	<50	4	8.0
	50-59	8	16.0
	60-69	11	22.0
	≥70	27	54.0
	Mean, 66.6; median 71.0		
Type of resection	Lobectomy	50	100.0
Lymph node dissection	ND1	2	4.0
	ND2	48	96.0
Histology	Adenocarcinoma	29	58.0
	SCC	19	38.0
	Others	2	4.0
Pathological TNM stage	IB	28	56.0
	IIA	10	20.0
	IIB	5	10.0
	IIIA	7	14.0

SCC, squamous cell carcinoma

Table 2 Drug Compliance (each course) (n = 50)

Course	No. of patients entering course	%	Reason for discontinuation
1	50	100	
			Grade 2 stomatitis (patient refusal)
			Recurrence
2	48	96.0	
			Grade 3 thrombocytopenia
			Grade2 thrombocytopenia and
			Grade 1 fever
			Grade 2 anorexia (patient refusal)
			Grade 2 anorexia (patient refusal)
			Grade 3 anorexia
			Grade 3 diarrhoea
			Grade 3 elevated total bilirubin
			Grade 2 anorexia (patient refusal)
3	40	80.0	
			Grade 1 anorexia and Grade 1 elevated
			total bilirubin (patient refusal)
			Patient refusal
			Change of hospital
4	37	74.0	
7			Stopped administration by mistake
8	36	72.0	
Complete			

Table 3 Adverse Reactions (n = 50)

	Grade				Total
	1	2	3	4	(incidence; percentage)
Laboratory findings					
Neutropenia	0	0	2	0	4.0
Leukocytopenia	1	4	0	0	10.0
Thrombocytopenia	1	4	1	0	12.0
Anemia	1	4	1	0	12.0
Increase in serum AST or ALT	1	0	0	0	2.0
Increase in serum total bilirubin	5	2	1	0	16.0
Hypokalaemia	0	0	1	0	2.0
Elevation of amylase	1	0	0	0	2.0
Clinical findings					
Fever	2	0	0	0	4.0
Anorexia	16	3	2	0	42.0
Nausea	3	2	1	0	12.0
Diarrhoea	2	0	1	0	6.0
Stomatitis	1	1	0	0	4.0
Malaise	1	1	0	0	4.0
Pigmentation	1	2	0	0	6.0
Constipation	1	1	0	0	4.0
Neural disturbance	1	0	0	0	2.0
Dehydration	0	1	0	0	2.0
Lacrimation	1	0	0	0	2.0

Grade 2 or more thrombocytopenia and other adverse reactions of Grade 3 or more match the criteria for dose reduction

Table 4 Effect of Dose Reduction on Adverse Reactions (n = 50)

	n	Completed cases	Completion rate (%)
Without adverse reaction	15	13	86.7
With adverse reactions	35	23	65.7
with dose reduction	24	19	79.2
without dose reduction	11	4	36.4