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ORIGINAL ARTICLE

Five-year outcomes of a phase II study of adjuvant chemotherapy with S-1 plus docetaxel for stage III gastric cancer after curative D2 gastrectomy (OGSG1002)

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Abstract

Background Adjuvant S-1 monotherapy is standard of care for stage II and III gastric cancer (GC), but there is still a need to improve the efficacy of treatment for stage III disease. We conducted phase II study of eight cycles of S-1 plus docetaxel (DS) followed by S-1 monotherapy for up to 1 year after D2 gastrectomy for stage III GC.

Patients and methods Sixty-two patients with stage III GC were enrolled. They received oral S-1 (80 mg/m^2/day) for 2 consecutive weeks and intravenous docetaxel (40 mg/m^2) on day 1, repeated every 3 weeks for 8 cycles, followed by S-1 until 1 year postgastrectomy. Treatment safety, tolerability, and survival were evaluated.

Results The completion rate for eight cycles of DS therapy was 77.4% [95% confidence interval (CI) 65.0–87.1%]. Subsequent S-1 monotherapy for 1 year was feasible in 71.0% (95% CI 58.1–81.8%) of patients. The incidence of neutropenia, leukopenia, anorexia, and fatigue of grade 3 or higher was 10% or higher. There were no treatment-related deaths. The 5-year overall survival (OS) and disease-free survival (DFS) rates were 72.4% (95% CI 62.1–84.5%) and 60.0% (95% CI 48.8–73.9%), respectively. Subgroup analyses by disease stage showed 5-year OS and DFS rates of 74.5% (95% CI 60.7–91.5%) and 59.3% (95% CI 43.8–80.2%) for stage IIIA and 70.0% (95% CI 55.4–88.5%) and 60.0% (95% CI 44.8–80.4%) for stage IIIB, respectively.

Conclusions Adjuvant eight cycles of DS therapy might be safe and manageable and has promising OS and DFS for stage III GC.

Keywords Adjuvant chemotherapy · S-1 · Docetaxel · Stage III gastric cancer · Five-year survival

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Introduction

Although several meta-analyses have suggested that adjuvant chemotherapy provides a survival benefit for gastric cancer [1–7], efficacy has been established for only a few treatments in large clinical trials. Postoperative radiotherapy with 5-FU plus leucovorin has become the standard adjuvant regimen in the United States [8], whereas the perioperative triplet regimen of epirubicin, cisplatin, and 5-FU is the standard in the United Kingdom [9]. In Japan and Korea, adjuvant chemotherapy with S-1 [10] or capecitabine plus oxaliplatin (XELOX) [11, 12] is the current standard of care after curative gastrectomy with D2 lymphadenectomy (D2 gastrectomy) for histologically confirmed stage II or III disease [13]. S-1 and XELOX are also recommended in the European Society for Medical Oncology (ESMO) guidelines [14]. Five-year follow-up data for adjuvant S-1 have been reported [15]. The S-1 group had a 5-year overall survival (OS) rate of 71.7%, compared with 61.1% in the surgery-alone group, corresponding to a 33% reduced risk of death [hazard ratio (HR) 0.669; 95% confidence interval (CI) 0.540–0.828]. However, approximately 35% of patients still develop recurrence despite adjuvant S-1; subgroup analyses have suggested that S-1 is less efficacious for stage IIIB gastric cancer (HR 0.791; 95% CI 0.520–1.205), in contrast to the clear survival benefit demonstrated for stage II and IIIA disease [15].

Several attempts have been made to improve the efficacy of adjuvant S-1 chemotherapy. Three cycles of S-1 plus cisplatin (SP) with subsequent S-1 monotherapy until 1 year after surgery was shown to be safe and manageable for stage III gastric cancer [16]. Recently, eight cycles of S-1 plus oxaliplatin (SOX) after surgery, in which S-1 alone was given in the first cycle and oxaliplatin was administered starting with the second cycle, was shown to be safe and tolerable as adjuvant chemotherapy for stage III gastric cancer [17]. On the other hand, four cycles of S-1 plus docetaxel (DS) followed by S-1 monotherapy for up to 1 year after surgery demonstrated promising OS with moderate toxicity in patients with stage III gastric cancer after curative D2 gastrectomy [18, 19]. Thus, identifying the more effective postoperative treatment for stage III disease has been the focus of public attention.

We conducted a phase II study to evaluate the safety, tolerability, and survival associated with eight cycles of DS followed by S-1 monotherapy for up to 1 year after surgery for stage III gastric cancer to determine if this regimen might be a potential candidate for the next phase III adjuvant chemotherapy trial.

Patients and methods

This study was a single-arm, prospective, multicenter phase II study at 14 centers in Japan. It was registered in the University Hospital Medical Information Network (UMIN) database (ID 000004440).

Eligibility

Eligibility criteria were as follows: histopathologically confirmed stage IIIA or IIIB gastric cancer; R0 resection with D2 or more extensive lymph node dissection; age 20–80 years; Eastern Cooperative Oncology Group performance status of 0–1; no previous treatment for cancer except for initial resection of the primary gastric lesion; adequate organ function including a leukocyte count between 3000 and 12,000 mm^3, neutrophil count $\geq$ 2000 mm^3, platelet count $\geq$ 100,000 mm^3, hemoglobin concentration $\geq$ 9.0 g/dL, aspartate aminotransferase and alanine aminotransferase levels $\leq$ 100 IU/L, serum bilirubin level $\leq$ 1.5 mg/dL, serum creatinine level $\leq$ 1.2 mg/dL, and creatinine clearance $\geq$ 60 mL/min; and provision of written informed consent. Exclusion criteria were as follows: synchronous or metachronous malignancies, difficulty with taking oral S-1; infection or suspected infection with fever; congestive heart failure; uncontrolled diabetes or hypertension; interstitial pneumonia or pulmonary fibrosis; symptomatic brain metastasis; liver cirrhosis or active hepatitis; severe drug hypersensitivity; peripheral sensory neuropathy; and pregnancy. Tumor stage classification and D classification were in accordance with the Japanese Classification of Gastric Carcinoma, second English edition [20]. All patients were also staged based on the seventh edition of the International Union Against Cancer TNM staging system [21]. Patients were enrolled within 6 weeks of surgery by facsimile.

Study design

Patients were given oral S-1 twice daily for 2 consecutive weeks with intravenous docetaxel (40 mg/m^2) on day 1, repeated every 3 weeks (1 cycle). The initial dose of S-1 was based on the body surface area (BSA) as follows: BSA < 1.25 m^2, 80 mg/day; 1.25 $m^2 \leq$ BSA < 1.5 m^2, 100 mg/day; and BSA $\geq$ 1.5 m^2, 120 mg/day. Before infusion of docetaxel, antiemetics (e.g., a 5-hydroxytryptamine3 receptor antagonist and dexamethasone) were administered prophylactically to prevent nausea and vomiting. Treatment was started within 45 days after surgery and repeated for eight cycles. After eight cycles of DS, S-1 monotherapy (4 weeks on, 2 weeks off) was continued until 1 year after surgery. DS treatment was continued for eight cycles unless any of the

discontinuation criteria were met: recurrence of the underlying cancer; inability to resume treatment within 2 weeks after the scheduled first day of the next cycle; requiring more than a two-level dose reduction for S-1 or docetaxel; inability to take S-1 for more than 8 days in the previous cycle; requiring a prohibited therapy; patient refusal of further treatment; or decision by the study investigator.

The doses of S-1 and docetaxel were reduced in the event of grade 3 neutropenia, grade 2 thrombocytopenia with active bleeding or any need for platelet transfusion, serum creatinine > 1.5 mg/dL, other drug-related nonhematological toxicities of grade 2 or higher, or any need of treatment suspension due to adverse effects. The dose was reduced by 5 mg/m^2 per level for docetaxel. If a third dose reduction of docetaxel was needed, treatment was discontinued. The dose of S-1 was reduced by one dose level (levels 1 and 2 were as follows: 50 and 40 mg/day for patients with a BSA < 1.25 m^2, 80 and 50 mg/day for patients with a 1.25 m^2 ≤ BSA < 1.5 m^2, and 100 and 80 mg/day for patients with a BSA ≥ 1.5 m^2).

The next cycle was only started if the following criteria were fulfilled: a neutrophil count ≥ 1500 mm^3, platelet count ≥ 75,000 mm^3, aspartate aminotransferase and alanine aminotransferase levels ≤ 100 IU/L, serum bilirubin level ≤ 2.0 mg/dL, serum creatinine level ≤ 1.5 mg/dL, and no non-hematological toxicities greater than grade 1. Otherwise, treatment was suspended for up to 2 weeks after the scheduled first day of the next cycle.

During each cycle, S-1 was discontinued if the patient developed a neutrophil count < 1000 mm^3, platelet count < 75,000 mm^3, aspartate aminotransferase or alanine aminotransferase level > 100 IU/L, serum bilirubin level > 3.0 mg/dL, serum creatinine level > 1.5 mg/dL, or non-hematological toxicity of grade 2 or higher.

Follow-up

Patients underwent hematology tests, biochemistry tests, and assessments of clinical symptoms and signs at least once during each cycle of DS and at 6-week intervals during S-1 monotherapy. From the second year onward, all patients were followed at least every 3 months. Relapse was confirmed by imaging studies, including ultrasonography, computed tomography, as well as gastrointestinal endoscopy. Patients underwent abdominal computed tomography at intervals of 6 months or less for the first 3 years after surgery and at 1-year intervals thereafter until 5 years after surgery. Patients also underwent gastrointestinal endoscopy at 1-year intervals. All patients were followed up for at least 5 years from the date of treatment initiation or until death. None were lost to follow-up. Adverse events were evaluated according to the Common Toxicity Criteria for Adverse Events, version 3.0.

Statistical analysis

The primary end point was the treatment completion rate, which was defined as the percentage of patients who completed eight cycles of DS therapy. The secondary endpoints were safety, disease-free survival (DFS), OS, and feasibility of S-1 administration until 1 year after surgery.

The sample size was calculated with an expected feasibility rate of 68% and a threshold feasibility rate of 50% for eight cycles of DS treatment based on a two-sided alpha level of 0.05 and statistical power of 80%. The planned sample size was 60 patients, allowing for dropout by two patients.

Safety was assessed in all patients who received at least one dose of S-1 or docetaxel (safety analysis set). The treatment completion rate and the ratio of the delivered dose to the planned dose were analyzed for patients in the safety analysis set who met the eligibility criteria (full analysis set).

OS and DFS for up to 5 years from the date of treatment initiation were estimated for all patients and analyzed by disease stage. OS was defined as the time from the date of treatment initiation to the date of death from any cause or last follow-up. DFS was defined as the time from the date of treatment initiation to the date when recurrence or a second malignancy was confirmed, death from any cause, or last follow-up, whichever came first. Survival curves were estimated using the Kaplan–Meier method, and the 95% CIs for survival rate were estimated using Greenwood's formula. All statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC, USA).

The planned dose was defined as the total dose if eight cycles had been completed without dose reduction. As an exploratory analysis, we also assessed the relative dose intensity (RDI), which was defined as the ratio of delivered dose intensity to the planned dose intensity. Dose intensity was calculated as the ratio of the cumulative dose to the treatment duration per 21 days.

Subgroup analyses of tolerability and RDI were performed. The subgroups were defined on the basis of the following baseline patient characteristics: age (younger than 65 years vs. 65 years or older), type of gastrectomy, and weight change within the first month after surgery (loss of less than 15% vs. loss of 15% or more and loss of less than 10% vs. loss of 10% or greater).

Results

Patients

Between December 2010 and December 2012, 62 patients (41 men and 21 women) with a median age of 63.5 years (range 30–79), were enrolled from 14 institutions in Japan.

According to the Japanese Classification of Gastric Carcinoma, 13th edition, 32 patients (51.6%) had stage IIIA disease and 30 patients (48.4%) had stage IIIB disease. Total gastrectomy, proximal gastrectomy, and distal gastrectomy were performed in 24 patients (38.7%), 3 patients (4.8%), and 35 patients (56.5%), respectively. Patient characteristics are listed in Table 1. All patients were included in the safety and full analysis sets.

Table 1 Patient characteristics

	Patients ($n=62$)
Age (years)	
Median (range)	63.5 (30–79)
Gender	
Male	41
Female	21
ECOG PS	
0	44
1	18
Pathological type	
Intestinal	25
Diffuse	37
Stage[a]	
IIIA	32
IIIB	30
pT stage[b]	
pT2	3
pT3	18
pT4a	37
pT4b	4
pN stage[b]	
pN0	2
pN1	5
pN2	20
pN3a	24
pN3b	11
M stage[b]	
M0	62
M1	0
Stage[b]	
IIB	2
IIIA	13
IIIB	24
IIIC	23
Surgical procedure	
Total gastrectomy	24
Proximal gastrectomy	3
Distal gastrectomy	35

ECOG PS Eastern Cooperative Oncology Group performance status

[a]Japanese classification, 13th edition

[b]TNM classification, 7th edition

Feasibility

Forty-eight patients completed the eight planned cycles of treatment. The treatment completion rate was 77.4% (48/62; 95% CI 65.0–87.1%), which was higher than the threshold completion rate of 50.0% ($P < 0.001$). In 14 patients who could not complete treatment, reasons for treatment discontinuation were as follows: treatment could not be resumed more than 2 weeks after the scheduled first day of the next cycle in 5 patients (because of neutropenia in 3 patients, worsening of complicating disease in 1 patient, and upper respiratory infection in 1 patient), requiring more than a 2-level dose reduction of S-1 or docetaxel in 2 patients, inability to take S-1 for more than 8 days in the previous cycle in 1 patient, investigator decision to discontinue treatment in 2 patients, refusal of further treatment by 2 patients, and recurrence in the liver and lung, respectively, in 1 patient each.

Forty-eight patients completed eight cycles of DS, but four patients did not complete the subsequent planned S-1 monotherapy: two due to recurrent cancer, one due to other malignancy, and one due to physician decision. The completion rate for eight cycles of DS and subsequent S-1 monotherapy for 1 year was 71.0% (44/62; 95% CI 58.1–81.8%). RDI for S-1 and docetaxel for eight cycles of chemotherapy were 80.9% and 82.5%, respectively. Moreover, the compliance rate for S-1 was 95.8% (46/48; 95% CI 85.8–99.4%) and 91.7% (44/48; 95% CI 80.0–91.7%) at 9 and 12 months after surgery, respectively.

Thirty-nine patients (63%) required S-1 dose reduction and 12 patients (19%) had dose reduction of two dose levels. In all of these patients, dose reduction was due to adverse events, mainly neutropenia, except for one patient with significant weight loss. Thirty-five patients (56%) required docetaxel dose reduction and 11 patients (18%) had reduction of two dose levels. The main reason for dose reduction was an adverse event, mainly neutropenia.

Thirty-seven patients (60%) experienced a delay in the initiation of a subsequent cycle of DS therapy. Eight of 60 patients (13%) experienced a delay after the first cycle, 9 of 59 patients (15%) after the second cycle, 10 of 58 patients (17%) after the third cycle, 7 of 56 patients (13%) after the fourth cycle, 7 of 55 patients (13%) after the fifth cycle, 13 of 53 patients (25%) after the sixth cycle, and 9 of 51 patients (18%) after the seventh cycle. The most common reason for a delay in administration was an adverse event, mainly neutropenia.

Safety

Adverse events of all grades are shown in Table 2. The most frequent grade 3–4 hematological toxicity during eight

Table 2 Hematological and nonhematologic adverse events of chemotherapy

Toxicity	NCI CTC grade ($n=62$)					
	1	2	3	4	3–4 (%)	4 (%)
Leukopenia	7	22	14	1	24	2
Neutropenia	2	7	21	12	53	19
Anemia	24	17	0	0	0	0
Thrombocytopenia	7	0	0	0	0	0
Febrile neutropenia	0	0	0	0	0	0
AST/ALT	12	1	0	0	0	0
T-Bil	2	5	1	0	2	0
Cr	3	0	0	0	0	0
Stomatitis	5	2	0	0	0	0
Diarrhea	11	7	2	0	3	0
Anorexia	12	17	11	0	18	0
Nausea	13	18	1	0	2	0
Vomiting	5	8	0	0	0	0
Fatigue	11	18	6	0	10	0
Alopecia	7	2	0	0	0	0
Fever	4	4	0	0	0	0
Sensory neuropathy	8	4	0	0	0	0

NCI CTC National Cancer Institute Common Toxicity Criteria, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *T-Bil* total bilirubin, *Cr* creatinine

cycles of this regimen was neutropenia, which was observed in 33 of 62 patients (53%). Another grade 3–4 hematological toxicity, leukopenia, occurred in 15 patients (24%). Nonhematological toxicities of grade ≥ 3 included anorexia in 18%, fatigue in 10%, diarrhea in 3%, nausea in 2%, and elevated total bilirubin in 2% of patients. No grade 4 nonhematological toxicities were observed in any patient. Peripheral sensory neuropathy developed in 12 patients (19%), but all events were of grade 2 or lower. There were no serious adverse events requiring hospitalization or treatment-related deaths within 30 days after treatment completion.

Survival

Survival analyses were performed on all patients. Eighteen patients died, of whom 16 died of disease relapse and 2 from other causes such as cardiac failure and pneumonia. Twenty-two patients had recurrence, and two patients developed a second malignancy (one breast cancer, one lung cancer). The 5-year OS and DFS rates for all patients were 72.4% (95% CI 62.1–84.5%) and 60.0% (95% CI 48.8–73.9%), respectively (Fig. 1a, b). Kaplan–Meier estimates of 5-year OS and DFS rates are shown by disease stage, with 5-year OS rates of 74.5% (95% CI 60.7–91.5%) and 70.0% (95% CI 55.4–88.5%) for stages IIIA and IIIB disease (Fig. 2a), respectively. The 5-year DFS rates were 59.3% (95% CI 43.8–80.2%) and 60.0% (95% CI 44.8–80.4%) for stages IIIA and IIIB disease, respectively (Fig. 2b). In addition, the 5-year recurrence-free survival (RFS) rate for all patients was 61.6% (95% CI 60.1–83.0%), with 5-year RFS rates of 62.2% (95% CI 46.7–82.9%) and 60.0% (95% CI 44.8–80.4%) for stages IIIA and IIIB disease, respectively.

Site of relapse

Twenty-two patients had disease relapse involving nodal recurrence in 5 patients (1 mediastinal, 4 para-aortic), hematogenous recurrence in 6 patients (3 liver, 2 lung, 2 bone, 1 adrenal), and peritoneal dissemination in 13 patients.

Subgroup analyses

Results from exploratory subgroup analyses are shown in Tables 3 and 4. Two patients were lost with regards to weight loss. The treatment completion rate was 88.6% for patients younger than 65 years and 63.0% for patients aged 65 years or older. The treatment completion rate was 66.7% for patients who underwent total gastrectomy and 84.2% for those who underwent proximal or distal gastrectomy. The treatment completion rate was 80.5% for patients with < 10% weight loss and 68.4% for those with ≥ 10% weight loss.

Mean RDI for S-1 and docetaxel was higher in patients younger than 65 years than in patients aged 65 years or older (85.8% vs. 74.5% for S-1; 84.8% vs. 82.0% for docetaxel). Mean RDI for S-1 and docetaxel was lower in patients with total gastrectomy than in patients with proximal or distal

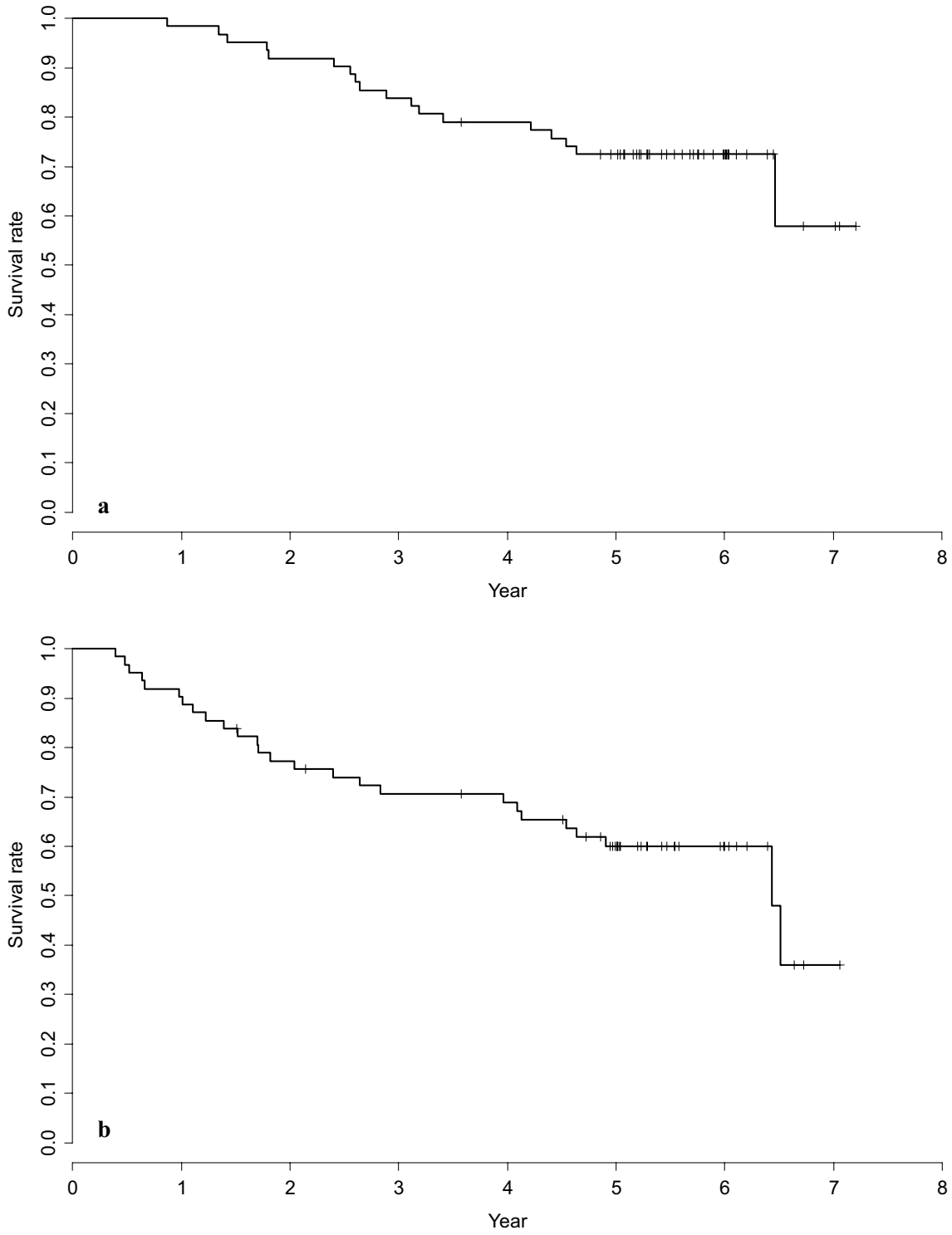

Fig. 1 Kaplan–Meier estimates of **a** 5-year overall survival and **b** 5-year disease-free survival for all patients

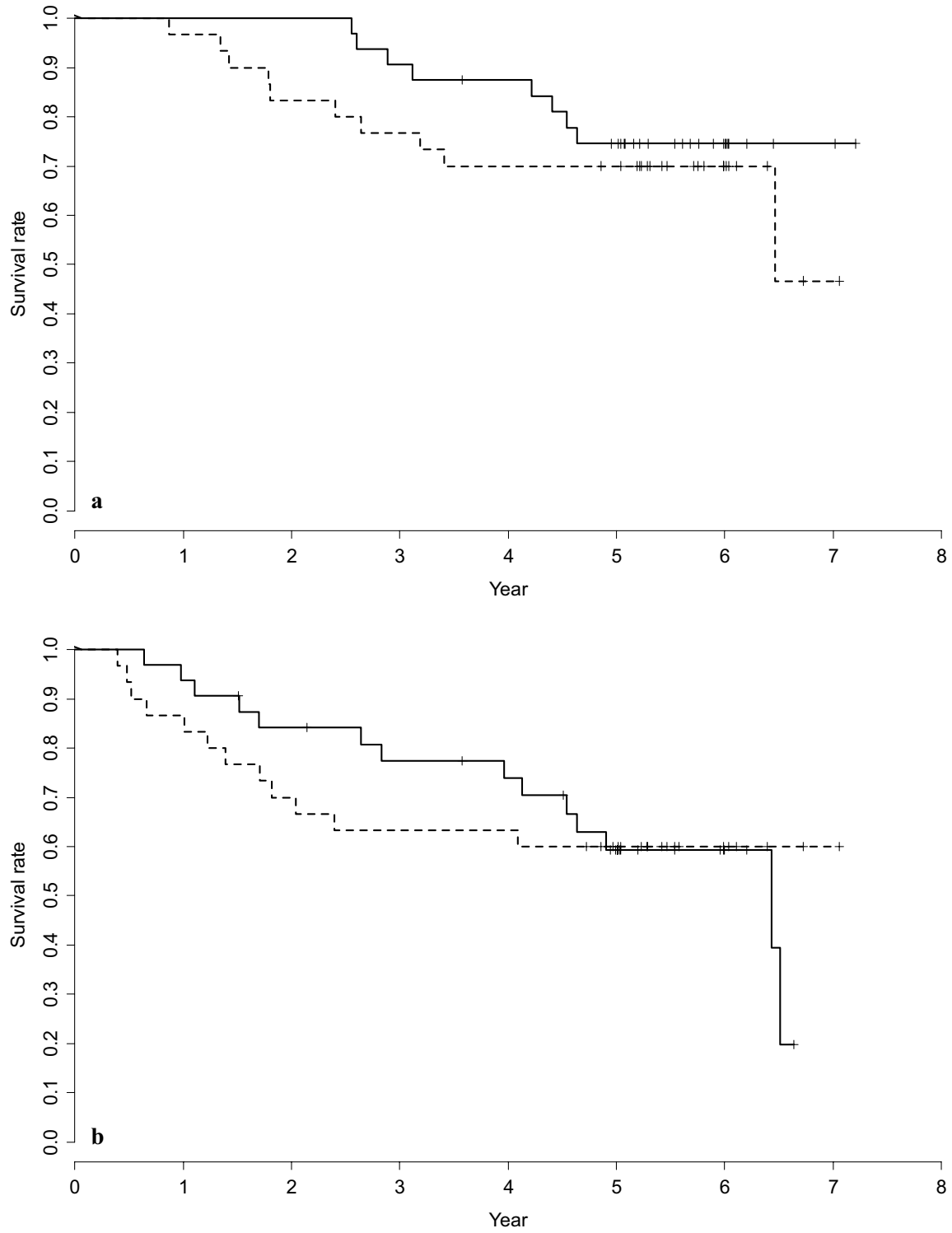

Fig. 2 Kaplan–Meier estimates of **a** 5-year overall survival and **b** 5-year disease-free survival for patients with stages IIIA (solid line) and IIIB (dotted line) gastric cancer

gastrectomy (72.3% vs. 86.3% for S-1; 75.9% vs. 86.7% for docetaxel). It was lower in patients with ≥ 10% weight loss than in those with < 10% weight loss (73.8% vs. 83.9% for S-1; 74.5% vs. 85.9% for docetaxel).

Table 3 Treatment completion rate

	Completion rate, *N*	Completion rate, % (95% CI)	Odds ratio (95% CI)
Age (years)			
< 65	31/35	88.6 (73.5–96.8)	4.442
≥ 65	17/27	63.0 (42.4–80.6)	(1.078–22.449)
Surgical procedure			
Total gastrectomy	16/24	66.7 (44.7–84.4)	0.381
Proximal/distal gastrectomy	32/38	84.2 (68.7–94.0)	(0.092–1.498)
Weight loss			
< 15%	45/58	77.6 (64.7–87.5)	3.372
≥ 15%	1/2	50.0 (1.3–98.7)	(0.041–276.934)
Weight loss			
< 10%	33/41	80.5 (65.1–91.2)	1.882
≥ 10%	13/19	68.4 (43.4–87.4)	(0.445–7.686)

N patient number, *CI* confidence interval

Table 4 Relative dose intensity

	No. of patients	S-1 Mean percentage	Docetaxel Mean percentage
Age (years)			
< 65	35	85.8	84.8
≥ 65	27	74.5	82.0
Surgical procedure			
Total gastrectomy	24	72.3	75.9
Proximal/distal gastrectomy	38	86.3	86.7
Weight loss			
< 15%	58	80.6	82.4
≥ 15%	2	83.3	78.0
Weight loss			
< 10%	41	83.9	85.9
≥ 10%	19	73.8	74.5

Discussion

The mainstay of treatment for gastric cancer is surgery. However, in stage II and III disease, quite a few patients experience recurrence, even after curative resection. Adjuvant chemotherapy is used to prevent distant or local recurrence and improve survival. A recent meta-analysis by the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) group [7] showed that postoperative adjuvant chemotherapy is associated with an 18% risk reduction in terms of DFS (HR 0.82; 95% CI 0.75–0.90) and OS (HR 0.82; 95% CI 0.76–0.90) compared with surgery alone in patients with resectable gastric cancer. One year of S-1 monotherapy after D2 gastrectomy has been established as the standard of care in Japan for patients with stage II or III gastric cancer, with a 33% reduced risk of death (HR 0.669; 95% CI 0.540–0.828) [15], which was comparable to the mortality risk reduction of 26% obtained with postoperative chemoradiotherapy in the United States [8] and the 25% obtained with perioperative triplet chemotherapy in the United Kingdom [9]. However, approximately one-third of patients still relapse despite adjuvant treatment with S-1. Subgroup analyses have shown that S-1 has insufficient efficacy for stage IIIB disease (HR 0.791; 95% CI 0.520–1.205) [15], suggesting that some room for improvement remains. To improve the efficacy of adjuvant chemotherapy, other agents such as cisplatin [22], oxaliplatin [23, 24], and docetaxel [25, 26], which has shown effective cytotoxicity against advanced gastric cancer in several randomized controlled trials, have each been investigated in combination with S-1 for feasibility and survival in the adjuvant setting.

The incidence of neutropenia, leukopenia, anorexia, and fatigue of grade 3 or higher was 10% or higher in this study, which did not differ greatly from our previous study of four cycles of DS therapy [19] or a recent study of six cycles of DS therapy [27]. However, neutropenia and leukopenia of grade 3 or greater were more common than with eight cycles of SOX therapy [17]. Due to adverse events, mainly neutropenia, 39 of 62 patients (63%) and 35 of 62 patients (56%) required dose reduction of S-1 and docetaxel, respectively, and 37 of 62 patients (60%) required a delay in chemotherapy administration. Although approximately half of the patients required dose reduction or delay, mean RDI was 80.9% for S-1 and 82.5% for docetaxel in this study. Furthermore, eight cycles of DS followed by S-1 monotherapy for up to 1 year showed superior feasibility of 77.4% (95% CI 65.0–87.1%) for eight planned cycles of DS and good compliance with S-1 monotherapy at 12 months after surgery in

71.0% patients. The treatment completion rate of 77.4% was comparable to rates of 79.2%, 74.2%, and 81.1% obtained with four cycles of DS therapy [19], eight cycles of SOX therapy [17], and three cycles of SP therapy [16], respectively. S-1 compliance of 71.0% at 12 months was compatible with 65.8% in the ACTS-GC trial that established 1 year of adjuvant S-1 monotherapy as the Japanese standard of care [10]. Thus, adverse events did not have a marked influence on the feasibility of eight cycles of adjuvant DS therapy by the optimal management throughout the entire study.

With regard to the treatment completion rate and RDI, age younger than 65 years seemed to have a positive effect, whereas total gastrectomy and postoperative weight loss likely had a negative impact in this study. In patients with total gastrectomy, anorexia and fatigue of grade 3 or higher were more common than the others (29% vs. 11%, 17% vs. 5%). Likewise, in patients with ≥ 10% weight loss, neutropenia and anorexia of grade 3 or worse were more common than the others (68% vs. 46%, 21% vs. 15%). However, there are some controversies about risk factors for poor compliance with adjuvant chemotherapy for gastric cancer. Aoyama et al. reported that weight loss over 15% at 1 month after surgery, but not age or type of gastrectomy, is significantly correlated with low compliance with adjuvant S-1 therapy [28, 29]. Yamashita et al. suggested that age over 65 years, but not type of gastrectomy or weight loss, was an independent risk factor for poor compliance with adjuvant S-1 chemotherapy [30]. Total gastrectomy affected compliance with adjuvant SOX treatment, but age did not [17]. These potential risk factors should be taken into account because lower compliance with adjuvant chemotherapy might cause unfavorable prognosis.

Eight cycles of DS therapy yielded 5-year OS rates of 74.5% (95% CI 60.7–91.5%) and 70.0% (95% CI 55.4–88.5%) for stages IIIA and IIIB disease (Fig. 2a), respectively, compared with 67.1% and 50.2% for S-1 monotherapy in the ACTS-GC trial [15]. Thus, adjuvant chemotherapy with eight cycles of DS followed by S-1 monotherapy until 1 year after surgery is expected to have a survival benefit over S-1 monotherapy for stage III disease.

An extremely strong correlation between 3-year DFS and 5-year OS was demonstrated by the GASTRIC group meta-analysis of 14 adjuvant trials after curative resection of gastric cancer [31]. In recent large clinical trials of adjuvant chemotherapy after curative D2 gastrectomy, 3-year RFS or 3-year DFS has been evaluated as a surrogate measure of 5-year OS [10, 27, 32] because 3-year RFS has also been proven to become the primary end point for potentially curable gastric cancer, confirming the strong concordance of 3-year RFS with 5-year OS [15]. In this study, eight cycles of DS therapy resulted in a 3-year RFS of 70.6% (95% CI 60.1–83.0%) (data not shown), whereas it was 70.9% (95% CI 57.8–80.5%) for eight cycles of SOX [33] and 66% (95% CI 59–73%) for six cycles of DS [27], respectively, which suggests the equal power of these three adjuvant regimens. As different stage classification were used between the current study and other trials, the results should be interpreted cautiously. Furthermore, when comparing the current eight cycles to our previous four cycles of DS therapy [18] with the same patient eligibility criteria, eight cycles of DS therapy yielded better 3-year DFS rates of 77.4% and 63.3% for stages IIIA and IIIB disease (data not shown), respectively, compared with 70.8% and 56.2% for four cycles of DS therapy [18].

So far, 22 out of 62 patients (35.5%) have relapsed in this study, consisting of nodal recurrence in 8.1%, hematogenous recurrence in 9.7%, and peritoneal dissemination in 21.0% of patients, compared with a total of 30.6% of patients who developed recurrences with adjuvant S-1 monotherapy after D2 gastrectomy in the ACTS-GC trial with the peritoneum (14.6%), hematogenous sites (11.5%), and lymph nodes (5.7%) as common sites of relapse [15]. Among the patients treated with 8 cycles XELOX [11] or 6 cycles DS therapy [27], the common site of first recurrence was the peritoneum in 10.2% or 9.3% of patients, hematogenous sites in 12.1% or 5.3%, and the lymph node in 5.2% or 4.8%, respectively. As inclusion criteria of the stage, stage classification, and proportion of the stages IIIA and IIIB were different between the current study and other trials, the results should be interpreted cautiously.

In conclusion, this 5-year follow-up study suggests that postoperative adjuvant chemotherapy with eight cycles of DS followed by S-1 monotherapy for up to 1 year after D2 gastrectomy is safe and efficacious in patients with stage III gastric cancer. However, this study is a small-scale phase II study, not large enough to draw definitive conclusions on the benefits of DS over S-1 monotherapy for stage III gastric cancer. Superior feasibility of this combined regimen in the adjuvant setting and promising OS and DFS warrant a future phase III trial (eight cycles of DS versus S-1 monotherapy) to identify the optimal adjuvant chemotherapy regimen for stage III gastric cancer.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement/Human rights statement and informed consent All study procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Written informed consent or substitute for it was obtained from all patients for inclusion in the study.

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