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ORIGINAL ARTICLE

Safety evaluation of oral fluoropyrimidine S-1 for short- and long-term delivery in advanced gastric cancer: analysis of 3,758 patients

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Abstract
Purpose To evaluate the comprehensive safety profile of S-1, a promising novel oral fluoropyrimidine derivative, based on large cohort data.
Patients and methods Study subjects were identified from a prospective registry of 3,758 advanced gastric cancer patients in Japan. Each patient was treated with an identical regimen of S-1 monotherapy (40 mg b.i.d. on days 1–28, every 6 weeks) and assessed for all adverse events.
Results The median duration of treatment was 88 days; 1,605 (43%) patients underwent three or more treatment cycles. The relative dose intensity was 0.87 in the first two cycles (short-term treatment period) and 0.89 thereafter (long-term treatment period). Neutropenia was the most common severe (grade 3–4) hematological event (6.3% in the short-term period and 5.3% in the long-term period). Other hematological or key gastrointestinal events (diarrhea, nausea/vomiting, and stomatitis) had a low incidence of severe cases throughout the whole administration period (0.3–3.8%). The time to onset of severe events did not differ between patients with mild renal impairment (creatinine clearance, 50–79 ml/min) and those with normal renal function (≥80 ml/min) (hazard ratio, 1.04; 95% CI, 0.87–1.23; $P = 0.691$).
Conclusions S-1 had manageable severe toxicity and allowed good compliance regardless of treatment duration. Prolonged administration of the drug was sustainable.

Keywords Gastric cancer · S-1 · Adverse events · Renal function · Capecitabine

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Introduction

S-1 is a novel oral fluoropyrimidine derivative that is currently used in Japan for the treatment of various solid tumors, including gastrointestinal, lung, head and neck, breast and pancreatic carcinomas. S-1 was designed on the basis of the biochemical modulation of 5-fluorouracil (5-FU) and comprises tegafur and two enzyme inhibitors, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo), in a molar ratio of 1:0.4:1 [1].

In two phase II studies of S-1 monotherapy in patients with advanced gastric cancer, response rates were 49 and 44%, respectively [2, 3]. These results were the highest response rates in phase II studies of new-generation agents for the treatment of advanced gastric cancer, while other such agents (irinotecan, docetaxel, paclitaxel, and capecitabine) exhibited moderate activity and yielded response rates of 18–34% [4–8]. Recent studies in both Japan and the West have reported that both excellent response rates exceeding 50% and prolonged median survival times (MSTs) were achieved with a combination of S-1 and cisplatin, irinotecan, or taxane [9–13]. This accumulating evidence suggests that the effectiveness of S-1 is at least

equivalent to, if not better than, continuous intravenous or bolus administration of 5-FU and other oral fluoropyrimidines. Accordingly, either S-1 monotherapy or S-1 coupled with another agent has become one of the standard first-line treatments for advanced gastric cancer in Japan. Recent interest in the drug has also been considerable in the West [14], especially after the recent announcement of positive results in randomized phase III studies (ACTS-GC and JCOG9912 trials).

The clinical use of S-1 in medical practice began with a nationwide prospective registry in Japan, conducted by the manufacturer (Taiho Pharmaceuticals, Tokyo, Japan) in 1999, in which advanced gastric cancer patients undergoing S-1 were enrolled. The primary scope of this registry was to collect as wide a range of safety profile data as possible since clinical trials are limited in obtaining such information because of small to moderate sample size. The registry, in fact, performed a complete registration of all patients scheduled for treatment by S-1 and, eventually, collected data from a total of 3,758 patients. Such an investigation facilitated the generation of a reliable safety profile of the drug in practice. A previous article reported adverse events during the first two cycles of this registry that involved a possible causal relation between S-1 and each event (that is, adverse drug reactions) [15]. However, the median duration of treatment in the registry was two cycles and nearly 50% of the registered patients underwent S-1 administration for three or more cycles. This observation implied that toxicity of long-term drug delivery over two cycles needed to be evaluated in the registry. Moreover, other crucial points, including drug compliance, time to onset of toxicity, and negative impact of renal impairment, also needed to be analyzed to better develop S-1 in the clinic. At present, no study has answered these issues based on a sufficiently large body of data. In this regard, the current registry provided a valuable channel for the comprehensive understanding of the safety of the drug. The purpose of this article is to report the results of our integrated analysis on the entirety of the registry data, along with all recorded adverse events in the whole treatment period regardless of possible causal relation with the drug by investigators.

Methods

Patients

All patients who were scheduled for treatment by S-1 between March 1999 and March 2000 were enrolled in the registry. Each patient was provided S-1 upon confirmation of enrollment by the central data center. To ensure safe use of S-1, the following nine criteria were required for patient registration: Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2; leucocyte count $\geq 4{,}000/mm^3$ and $\leq 12{,}000/mm^3$; neutrophil count $\geq 2{,}000/mm^3$; platelet count $\geq 100{,}000/mm^3$; hemoglobin level ≥ 9.0 g/dl; creatinine $\leq$ upper limit of normal range (ULN); and hepatic functions [total bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST)] $\leq 2 \times$ ULN. However, since the registry was conducted under general practice conditions, patients who did not satisfy all of the above criteria were allowed to be enrolled but under careful monitoring in order to make the registered patients reflect the general population of advanced gastric cancer. Patients satisfying all nine criteria were classified as the *appropriate-use* group.

The registry was conducted under the same protocol at all participating centers, and informed consent was obtained from all the patients prior to enrollment. Data collection and management were carried out at the central data center. Patients were followed up until either March 2002 or death.

Treatment delivery

The initial dose of S-1 was based on the patient's body surface area (BSA) as follows: BSA $< 1.25\ m^2$, 40 mg; BSA $\geq 1.25\ m^2$ and $<1.50\ m^2$, 50 mg; and BSA $\geq 1.50\ m^2$, 60 mg. The dose was taken twice a day orally after meals. A single treatment cycle consisted of S-1 monotherapy for 28 consecutive days, followed by 14 days of no treatment. This schedule was repeated every 6 weeks (42 days) unless the disease progressed or unacceptable adverse effects occurred. The dose modification was according to the scheme previously used in phase II studies [2, 3].

Dose intensity was calculated as the total dose administered divided by the duration of administration. The relative dose intensity (RDI) was then calculated as the ratio of the actual dose intensity to the ideal intensity, had the dose been administered as scheduled.

Safety assessment

For each patient, laboratory tests (hematological, hepatic, and renal) were performed every 2 weeks. Adverse events were assessed and recorded every 2 weeks and graded from 1 to 4 according to the criteria of the Japan Society of Clinical Oncology, which is equivalent to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) but with a few minor modifications to suit Japanese patients [16]. Our analysis was based on all recorded adverse events, regardless of whether or not the events were reported to be drug-related by investigators. Adverse events that occurred during the first two cycles were classified as *short-term* events, whereas those that occurred during or after the third cycle were classified as *long-term* events.

Renal impairment

The impact of baseline renal impairment on the safety profile was evaluated. Renal impairment was measured in terms of creatinine clearance calculated by the formula of Cockroft and Gault [17]. Renal function was then classified as normal (creatinine clearance ≥ 80 ml/min), mildly impaired (50–79 ml/min), moderately impaired (30–49 ml/min), or severely impaired (<30 ml/min).

Statistical analysis

The time to first onset of grade 3–4 adverse events was calculated by the Kaplan–Meier curve estimate, and the differences between curves were tested by logrank test. A stratified Cox regression model was used to analyze the association between renal function or initial S-1 dose and the time to onset of adverse events. Fisher's exact test was used to compare the frequencies of adverse events between patient subgroups. We reported all *P* values as two-sided, with *P* less than 0.05 indicating statistical significance. All analyses were performed using SAS for Windows (SAS Institute Inc, Cary, NC).

Results

Study population

A total of 4,177 patients with malignant tumors were registered from 757 institutions in Japan. Of these, 419 were excluded because they did not receive S-1, had different malignancies other than gastric tumors, or had undergone complete resection of gastric cancer. The study population for our analysis thus comprised 3,758 advanced gastric cancer patients. Table 1 shows the demographics of these patients, which closely resemble those of patients in previous phase II studies [2, 3].

Table 1 Characteristics of study population (n = 3,758)

Characteristics	
Age	
Median (range)	63 (18–92)
Sex	
Male	2,624 (70%)
Female	1,134 (30%)
BMI	
Median (range)	19.5 (12.3–33.5)
ECOG performance status	
0	2,263 (60%)
1	1,207 (32%)
2	270 (7%)
3/4	17/1 (0.5%)
Disease status	
Advanced	2,153 (57%)
Recurrent	1,605 (43%)
Creatinine clearance[a]	
≥80	1,379 (37%)
50–79	1,811 (48%)
30–49	530 (14%)
<30	38 (1%)
Eligibility status	
Appropriate-use[b]	2,747 (73%)
Other	1011 (27%)
Prior chemotherapy[c]	
No	1,831 (49%)
Yes	1,927 (51%)

Unit: age (years), BMI (kg/m^2), creatinine clearance (ml/min)

BMI body mass index, *ECOG* Eastern Cooperative Oncology Group

[a] Calculated by the Cockcroft-Gault formula

[b] Patients satisfying all of nine criteria at baseline (refer to the Methods section)

[c] Chemotherapy history within half a year prior to S-1

Summary of S-1 delivery

Table 2 describes the summary of S-1 delivery. The median duration of treatment for the 3,758 patients was 88 days (two treatment cycles); 43% of the patients (1,605 out of 3,758) underwent treatment for three or more cycles and were classified as *long-term administered* patients. Conversely, the treatment discontinuation rate in the first two cycles was 57% (2,153 out of 3,758); treatment was discontinued in 17% (650 out of 3,758) due to adverse events and in 40% (1,503 out of 3,758) due to death or disease progression. For the 1,605 long-term administered patients, the discontinuation rate due to adverse events was 8% (127 out of 1,605). Thus, throughout the total length of the registry, treatment was discontinued in 777 (650 + 127) patients due to adverse events, which was 21% of the total number enrolled. The number of patients whose treatment was initiated at a lower dose than the standard dose (see 'Initial dose < Standard' in Table 2) was 928 (395 + 533), which was 25% of the total number enrolled, and in 739 of these patients, treatment was actually initiated with a one-level dose reduction.

Treatment discontinuation was more frequent in the subgroup of patients who had received chemotherapy within half a year and initiated S-1 at a lower dose than the standard dose (see the bottom row in Table 2). This finding was due to high mortality and disease-progression rates observed within the first two cycles for this subgroup (48%), compared with the other three subgroups (39%) ($P < 0.001$, Fisher's exact test).

Table 2 Summary of S-1 delivery

Prior chemotherapy[a]	Initial dose status	No.	Total treatment duration (days), median (range)	Long-term administered[b], no. (%)	RDI in short-term period[c], median (range)	RDI in long-term period[d], median (range)
All patients		3,758	88 (1–925)	1,605 (43%)	0.87 (0.09–1.43)	0.89 (0.21–1.32)
No	Initial dose ≥ standard[e]	1,436	97 (1–925)	667 (46%)	0.96 (0.09–1.43)	0.96 (0.26–1.32)
	Initial dose < standard	395	90 (2–826)	182 (46%)	0.77 (0.20–1.05)	0.78 (0.27–1.05)
Yes	Initial dose ≥ standard	1,394	86 (1–882)	571 (41%)	0.95 (0.13–1.20)	0.94 (0.21–1.17)
	Initial dose < standard	533	84 (1–779)	185 (35%)	0.75 (0.17–1.37)	0.76 (0.24–0.96)

RDI relative dose intensity

[a] Chemotherapy history within half a year prior to S-1

[b] Patients undergoing three or more treatment cycles

[c] RDI for administration during the first two cycles

[d] RDI for administration during and after the third cycle

[e] Standard = dose determined according to body surface area

The median RDI of S-1 for the whole population was 0.87 in the short-term treatment period and 0.89 in the long-term treatment period (Table 2), indicating that the compliance of S-1 was good overall and was not reduced by prolonged treatment. The median RDI for patients whose treatment was initiated at the standard dose was approximately 0.95 regardless of the treatment period, showing a high completion rate of the scheduled dosing. On the other hand, the median RDI for patients whose treatment was initiated at a lower dose than the standard dose was less than 0.80. The total dose administered to these patients obviously remained low, compared with an ideal value that assumes the initiation of S-1 at a standard dose, thus leading to a decrease in RDI.

Comparison of adverse events between short- and long-term treatment periods

The adverse events that occurred at a frequency of ≥10% (all grades) in either the short-term or long-term treatment periods are listed in Table 3. Anorexia (37% in the short-term period, 43% in the long-term period), fatigue (28, 33%), nausea/vomiting (26, 26%), leucopenia (27, 25%), and neutropenia (22, 23%) occurred in ≥20% of the patients in both the short- and long-term treatment periods (all grades). Grade 3–4 adverse events that occurred with a frequency of ≥5% in both the short- and long-term treatment periods were anorexia (11, 10%), fatigue (8, 8%), and neutropenia (6, 5%). The levels of liver enzymes increased with prolonged administration of S-1 [total bilirubin (T-bil), 13→21%; AST, 10→17%; ALT, 8→11%; and alkaline phosphatase (ALP), 10→17%; all grades]. However, these levels were almost unchanged for grade 3–4 events (T-bil, 4→7%; AST, 1→2%; ALT, 1→1%; ALP, 2→3%), indicating that there was no evidence of direct hepatotoxicity by S-1. Anorexia was the most frequently occurring grade 3–4 event although the incidence of other grade 3–4 gastrointestinal tract events (nausea/vomiting, diarrhea, and stomatitis) remained low in both durations of treatment (0.3–3.8%). Grade 3–4 hematological events were infrequent with an incidence ranging from 1.5 to 6.3%. Overall, there were no differences between short- and long-term drug deliveries in the incidence of adverse events (Table 3).

Figure 1 shows the frequency of each severe outcome that occurred only with prolonged treatment, that is, the number of patients who never experienced any grade 3–4 events during the short-term treatment period but experienced events during the long-term treatment period. For each toxic event other than neutropenia and leucopenia, most of these patients did not experience even grade 1 or 2 events in the short-term treatment period. The frequency of key adverse events that are typically related to fluoropyrimidine treatment (neutropenia, diarrhea, nausea/vomiting, stomatitis, and dermal events) [18–20] was small (5–52 patients) as shown in Fig. 1.

Time to onset of severe adverse events

Table 4 lists the distribution of the time to first onset of each grade 3–4 adverse event among patients who experienced them. The median time to onset of severe hematological events (leucopenia, neutropenia, decreased hemoglobin, and thrombocytopenia) was approximately 3 weeks (22 days), identical to that of severe fluoropyrimidine-related key events (neutropenia, nausea/vomiting, diarrhea, stomatitis, rash, and pigmentation; 20 days). It is noteworthy that the median time to onset of severe hepatic events was 2 months; these events were delayed compared with other events. In contrast, the median time to onset of severe dermal events was only 2 weeks.

Table 3 Summary of adverse events with an incidence of 10% or more (all grades) in either short- or long-term treatment periods

Adverse event	Incidence in all grades		Incidence in grade 3–4	
	Short term (%)[a] (*n* = 3,758)	Long term (%)[b] (*n* = 1,605)	Short term (%) (*n* = 3,758)	Long term (%) (*n* = 1,605)
Hematological				
Leucopenia	26.9	25.4	2.8	1.5
Neutropenia	21.9	22.7	6.3	5.3
Hemoglobin decreased	12.1	14.8	2.3	2.4
Thrombocytopenia	9.8	8.8	2.0	2.1
Hepatic				
Total bilirubin increased	13.0	20.9	3.9	7.1
AST increased	10.0	16.6	1.4	2.2
ALT increased	8.0	10.7	0.9	1.1
ALP increased	9.9	17.4	2.2	2.9
Gastrointestinal				
Anorexia	37.1	43.2	10.7	10.0
Nausea/vomiting	26.2	25.5	3.8	2.9
Diarrhea	18.4	17.0	2.1	1.1
Stomatitis	12.8	8.8	1.2	0.3
Dermal				
Rash	9.0	5.4	0.9	0.2
Pigmentation	14.7	19.2	1.2	1.0
Other				
Fatigue	27.6	32.8	7.8	7.7

Thrombocytopenia and rash had an incidence of slightly less than 10%, but both are key events and included

[a] Incidence of each adverse event that occurred during the first two cycles

[b] Incidence of each adverse event that occurred during and after the third cycle

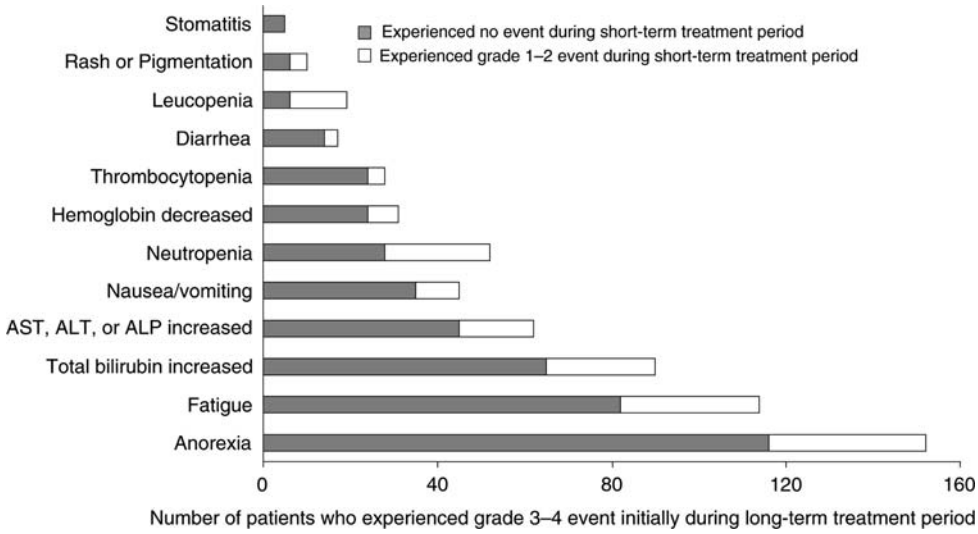

Fig. 1 The total number of patients who never experienced any grade 3–4 events during the short-term treatment period but did experience events during the long-term treatment period. The *dark bar* represents patients who did not experience any grade of events during the short-term period, while the *outlined bar* represents patients who experienced grade 1–2 events during the short-term period

Impact of renal impairment and initial dose on safety

The pharmacokinetics study of S-1 in both animal models and patients with impaired renal function reported that plasma clearance of CDHP and 5-FU is retarded according to the degree of renal impairment, suggesting that renal dysfunction may directly increase 5-FU concentration and lead to severe adverse events [21]. To assess and quantify the impact of baseline renal impairment and initial administered dose on the development of severe adverse events, the Kaplan–Meier curves that estimate the time to first onset were calculated. Figure 2 shows the estimated time to onset

Table 4 Distribution of time to onset of grade 3–4 adverse events

Adverse event	Total number of patients throughout study[a]	Distribution of time to first onset[b] (in days), median (quartiles)
Hematological		
Leucopenia	122 (3.2%)	20 (9, 58)
Neutropenia	287 (7.6%)	22 (12, 64)
Hemoglobin decreased	118 (3.1%)	32 (14, 86)
Thrombocytopenia	103 (2.7%)	36 (15, 101)
Hepatic		
Total bilirubin increased	235 (6.3%)	64 (22, 129)
AST increased	87 (2.3%)	68 (21, 137)
ALT increased	48 (1.3%)	52 (14, 127)
ALP increased	121 (3.2%)	38 (8, 106)
Gastrointestinal		
Anorexia	546 (14.5%)	37 (9, 92)
Nausea/vomiting	184 (4.9%)	40 (8, 85)
Diarrhea	96 (2.6%)	19 (12, 57)
Stomatitis	48 (1.3%)	12 (8, 41)
Dermal		
Rash	38 (1.0%)	12 (8, 21)
Pigmentation	49 (1.3%)	16 (10, 46)
Other		
Fatigue	400 (10.6%)	43 (15, 91)
Fluoropyrimidine-related key events[c]	632 (16.8%)	20 (9, 64)
Hematological events[d]	500 (13.3%)	22 (10, 71)

[a] Percentage in the parenthesis is the proportion to all (3,758) patients

[b] Distribution of time to first onset among patients who experienced each adverse event

[c] Neutropenia, nausea/vomiting, diarrhea, stomatitis, rash, pigmentation

[d] Leucopenia, neutropenia, hemoglobin decreased, thrombocytopenia

of grade 3–4 fluoropyrimidine-related key events (Fig. 2a) and its stratification according to status of both renal function (Fig. 2b) and initial dose of S-1 (Fig. 2c). Renal function was measured in terms of creatinine clearance. Patients exhibiting baseline renal impairment were confirmed to be at a significantly higher risk of grade 3–4 events ($P < 0.001$, logrank test); reduction of initial dose tended to diminish this risk ($P = 0.150$, logrank test). The same tendency was observed for grade 3–4 hematological events (results not shown). We applied a Cox regression model to quantify the impact of these factors in terms of hazard ratios (Table 5). Since the eligibility status of patients (whether they belonged to the appropriate-use group; refer to the Methods section) and the history of chemotherapy prior to S-1 would affect the risk of adverse events, the stratified Cox regression model with these two factors being strata was specifically used to eliminate their possible confounding effects [22]. The onset of severe fluoropyrimidine-related key events was significantly earlier in patients who exhibited moderate or severe renal impairment than in those with normal renal function (hazard ratio [HR], 1.46; 95% CI, 1.16–1.82; $P < 0.001$), translating into a 46% increase in the risk of these events. On the other hand, no differences were observed between patients with mild impairment and normal function (HR, 1.04; 95% CI, 0.87–1.23; $P = 0.691$). Reduction of initial dose contributed to a statistically significant decrease in the risk of adverse events (HR, 0.81; 95% CI, 0.67–0.98; $P = 0.034$). Similar results were observed for severe hematological events (Table 5). In summary, moderate or severe renal impairment elevated the risk of grade 3–4 episodes, while mild impairment did not. Lowering the initial dose of S-1 led to a reduction in the risk of adverse events.

Discussion

We set out to establish the safety profile of S-1 in the treatment of advanced gastric cancer using data from a prospective registry of 3,758 cases. The results of our analysis revealed that S-1 was associated with low incidence of adverse events. Also, prolonged administration of S-1 did not alter its safety profile in the short-term treatment period because most adverse events occurred with an approximately same incidence between the first two cycles and thereafter. Furthermore, the median RDI of the drug did not decline in the long-term treatment period but was maintained at a high value, implying that a dose reduction from the initial dose was not needed by most of the patients.

The incidence of severe key gastrointestinal events, such as diarrhea, stomatitis, or nausea/vomiting, was less than 5% in both the short- and long-term treatment periods. Severe myelosuppression (leucopenia, neutropenia, decreased hemoglobin, and thrombocytopenia), which was the reported dose-limiting toxicity in a phase I study [23], remained at 1.5–6.3% in both periods. Only total bilirubin showed a slight elevation of grade 3–4 outcomes with prolonged administration. Any grade of cardiac toxicity, neurotoxicity, and febrile neutropenia was rarely observed (<0.1%). S-1 was originally targeted at inducing fewer toxic effects while prolonging exposure to 5-FU [24–26], and our results supported such a concept.

Another oral fluoropyrimidine that has attracted considerable attention and can broaden the availability of the treatment of advanced gastric cancer is capecitabine [27]. Previously, three phase III studies on colorectal cancer have investigated the use of capecitabine monotherapy [18–20]; two of these studies were conducted for the first-line treatment of advanced cancer and one for the adjuvant treatment following surgery. Although the settings among the studies differed substantially, the drug safety profiles obtained were

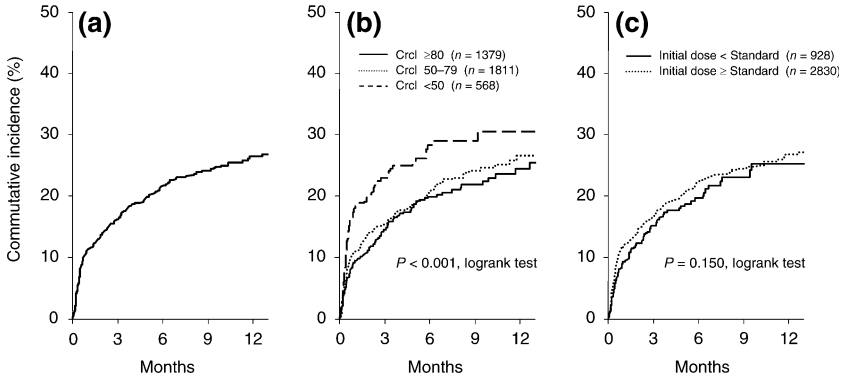

Fig. 2 Kaplan–Meier estimates for time to first onset of grade 3–4 fluoropyrimidine-related key adverse events (neutropenia, nausea/vomiting, diarrhea, stomatitis, rash, and pigmentation). The horizontal and vertical axes represent the time to onset (months) and the estimated probability of occurrence of the events, respectively: (**a**) estimate for all 3,758 patients; (**b**) stratification by status of renal function measured by creatinine clearance (Crcl); (**c**) stratification by status of initial dose of S-1

Table 5 Impact of baseline renal function and initial dose status on time to onset of grade 3–4 adverse events: multivariate Cox regression analysis

	Fluoropyrimidine-related key adverse events[a] (grade 3–4)			Hematological adverse events[b] (grade 3–4)		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Creatinine clearance						
≥80	1.00			1.00		
50–79	1.04	0.87–1.23	0.691	1.10	0.90–1.35	0.350
<50	1.46	1.16–1.82	<0.001	1.69	1.32–2.16	<0.001
Initial dose status						
≥ Standard	1.00			1.00		
< Standard	0.81	0.67–0.98	0.034	0.84	0.67–1.02	0.087

Multivariate Cox model stratified by *Eligibility status* and *Prior chemotherapy*

[a] Neutropenia, nausea/vomiting, diarrhea, stomatitis, rash, pigmentation

[b] Leucopenia, neutropenia, hemoglobin decreased, thrombocytopenia

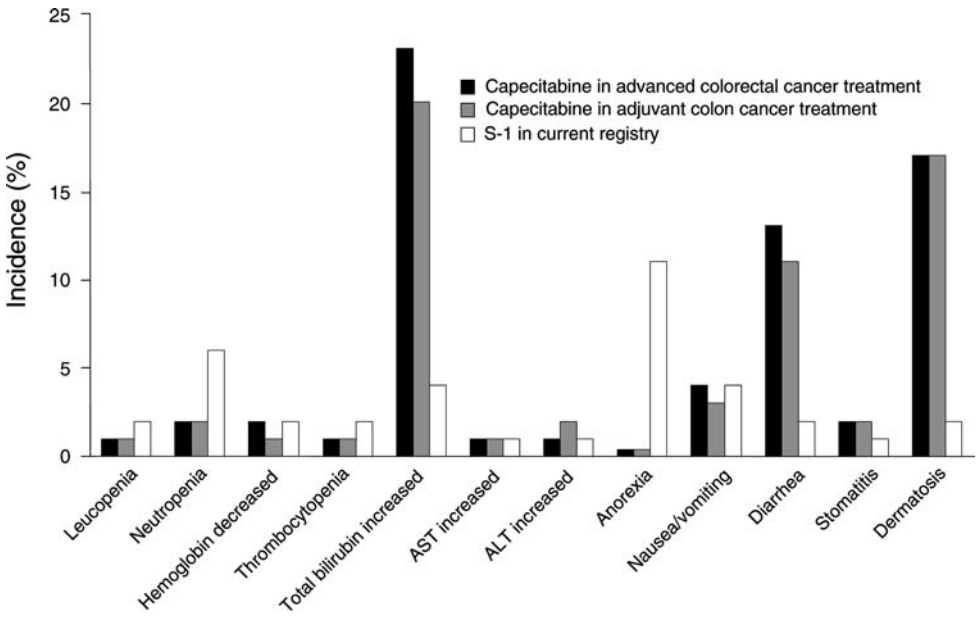

Fig. 3 Reported incidence of grade 3–4 adverse events of capecitabine in previous studies (advanced colorectal cancer [18, 19] and adjuvant colon cancer [20]) along with incidence of S-1 in our study. Adverse events of S-1 are those that occurred among patients who had no chemotherapy within 6 months, no major abnormalities in their laboratory parameters, and a good performance status at baseline (n = 1,365). Each incidence is rounded off and shown on the vertical axis

surprisingly similar [28, 29]. Thus, the data from these three studies that involved a total of 1,591 patients provided the safety profile of capecitabine monotherapy. Figure 3 shows the frequencies of major grade 3–4 events of capecitabine reported in the three studies as well as those of S-1 in our study. The three studies of capecitabine included several eligibility criteria for patient enrollment; therefore, in order to permit maximum comparability between our registry data and them, we focused on the 1,365 patients who had no chemotherapy within half a year prior to S-1 as well as belonged to the appropriate-use group and considered adverse events observed in this group.

Both capecitabine and S-1 were associated with a relatively low incidence of grade 3–4 hematological events (Fig. 3). A higher incidence of diarrhea was observed with capecitabine than with S-1, while anorexia was more common with S-1. Cutaneous events were much more common with capecitabine due to the occurrence of hand-foot syndrome (HFS), which is known as the most severe toxicity of capecitabine treatment [27]. The present study confirmed that S-1 rarely causes HFS. A major reason for this difference might be that CDHP in S-1 potently inhibits dihydropyrimidine dehydrogenase (DPD) and, in turn, decreases the concentration of F-β-alanine, which is a possible cause of HFS, neurotoxicity, and cardiotoxicity [30–33].

Previous articles have reported that patients with moderate or severe renal impairment at baseline exhibited a significantly higher incidence of adverse events with capecitabine treatment compared with those with normal renal function, although patients with mild impairment did not [28, 29]. Our analysis by the Cox regression model demonstrated that the same fact holds true for S-1 treatment. Thus, as in the case of capecitabine, S-1 could be initiated in patients with mild renal impairment at a standard dose under careful monitoring.

One crucial issue to be discussed is the applicability of our results for patients in Western countries because the registry included only Japanese patients. It has been reported that the MTD of S-1 is different in the West than in Japan, and that the toxicity profile appears to be different from Japanese studies, with more diarrhea and HFS, and less myelotoxicity [34]. Diarrhea was the dose-limiting toxicity in European patients [35], while HFS occurred in 3 out of 30 patients (one with grade 3 and two with grade 1) [34]. S-1 hardly causes severe cases in either events in Japanese patients as was shown in this registry. This difference might be due to the use of a different administration schedule and/or to genetic differences between the Asian and the Western populations. Careful consideration is required before applying our results to Western patients. However, treatment with S-1 is safe at a reduced dose with appreciable response rates. In the future, a different compounding ratio of tegafur, Oxo, and CDHP in S-1 may be desired in either population.

Gastric cancer is the fourth most commonly diagnosed cancer and the second leading cause of cancer death. Although gastric cancer patients typically exhibit an advanced phase of the disease, there is no internationally accepted standard treatment for this stage [36]. The rapid development of S-1 for gastric cancer both in Asia and the West shows promise for its use as a promising anticancer drug which may realize oral treatment and lead us into the next era of cancer management [37].

The present study from a large series of patients demonstrated the well-tolerated safety profile of S-1, suggesting that it is not inferior to capecitabine. Our results will contribute useful information for the future development of the combined use of S-1 with other agents.

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