S-1 as a core anticancer fluoropyrimidine agent

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Introduction: 5-FU is a core anticancer agent for GI and other malignancies, and infusional 5-FU regimens have been widely utilized. Orally administrable fluoropyrimidine prodrugs have been developed to enhance the anticancer efficacy of 5-FU and to reduce its adverse reactions.

Areas covered: S-1 is an FT-based oral 5-FU prodrug in combination with a DPD inhibitor (CDHP) and an OPRT inhibitor (Oxo), which exerts the following effects: i) maintaining normal gut immunity, Oxo can decrease GI toxicities of 5-FU; ii) sustaining high plasma 5-FU concentrations, Cmax of FBAL after S-1 administration is extremely low, which dramatically decreases adverse reactions such as HFS, neurotoxicities and cardiotoxicities; iii) plasma 5-FU concentrations vary less extensively after S-1 administration and iv) S-1 can be safely administered to patients with DPD deficiency. Furthermore, the alternate-day S-1 administration can reduce the GI toxicities and myelotoxicities of 5-FU without reducing its anticancer efficacy, enabling patients to continue the oral administration for 6 – 12 months.

Expert opinion: Replacement of regimens with infusional 5-FU and other fluoropyrimidines by the alternate-day S-1 administration may be recommended because the latter procedure is efficient for patients while sustaining the enhanced anticancer efficacy of 5-FU and without reducing its dose intensity.

Keywords: 5-fluorouracil prodrug, alternate-day administration, orally administrable fluoropyrimidines, S-1

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1. Introduction

Along with recent advances in diagnostic and therapeutic modalities, the multidisciplinary management of cancer treatments has been explored to obtain favorable outcomes [1-3]. After its development in 1957 [4], 5-fluorouracil (5-FU) (**Figure 1A**) has been widely used to treat various types of malignancies; in the internationally accepted standard regimens for gastrointestinal (GI) malignancies, 5-FU has been used as a core drug in all regimens except etoposide, doxorubicin and cisplatin (EAP) therapy. In the middle of 1960s, *in vitro* studies of 5-FU with cultured L1210 cells revealed that 5-FU is degraded very rapidly [5], and *in vivo* studies suggested that a longer interval of intravenous infusion than the S-phase of the cell cycle is preferable for 5-FU [6]. Since 5-FU is a time-dependent drug, regimens with long-term 5-FU infusion (continuous intravenous infusion of 5-FU (CVI 5-FU)), in which 5-FU is continuously infused for 1 week or longer, were designed. In the Mid-Atlantic Oncology Program Study in 1989 [7], the CVI 5-FU regimen significantly improved the response rate compared with the bolus 5-FU regimen (30 vs 7%, $p = 0.001$), and toxicity was substantially different for the two arms: leucopenia observed on the bolus 5-FU arm and hand-foot syndrome (HFS) only in the CVI 5-FU arm. In 1998, the meta-analysis of six randomized trials [8] revealed that CVI 5-FU was superior to bolus 5-FU in terms of tumor response and achieved a slight increase of overall survival (OS), and grade 3/4 hematologic toxicity was more frequent in patients assigned to the bolus 5-FU group than the CVI 5-FU group (31 vs 4%), whereas HFS was

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Article highlights.

- S-1 is a tegafur (FT)-based oral 5-fluorouracil (5-FU) prodrug in combination with a dihydropyrimidine dehydrogenase (DPD) inhibitor (5-chloro-2,4-dihydroxypyridine (CDHP)) and an orotate phosphoribosyltransferase (OPRT) inhibitor (potassium oxonate (Oxo)).
- Another fluoropyrimidine prodrug capecitabine has been approved in over 100 countries. On the other hand, S-1 has been used limitedly only in Japan and some other Asian countries.
- S-1 exerts the following effects: i) maintaining normal gut immunity, Oxo can decrease gastrointestinal (GI) toxicities of 5-FU; ii) sustaining high plasma 5-FU concentrations, Cmax of α-fluoro-β-alanine (FBAL) after S-1 administration is extremely low, which dramatically decreases adverse reactions such as hand-foot syndrome (HFS), neurotoxicities and cardiotoxicities; iii) plasma 5-FU concentrations vary less extensively after S-1 administration and iv) S-1 can be safely administered to patients with DPD deficiency because DPD is already inactivated by CDHP when S-1 is administered.
- To optimize the administration doses and schedules in Caucasians and Asians, ethnic differences in pharmacokinetics of S-1 have to be considered.
- Four-week administration of S-1 followed by 2-week withdrawal is the standard regimen in Japan. To reduce GI toxicities of patients, 2- or 3-week administration of S-1 followed by 1-week withdrawal has been proposed as an alternate schedule.
- The alternate-day S-1 administration can reduce the GI toxicities and myelotoxicities of 5-FU without reducing its anticancer efficacy, enabling patients to continue the oral administration of S-1 for 6 – 12 months.
- The alternate-day S-1 administration may give great benefits to Caucasians who experience more severe GI toxicity for FT due to their high activity of *CYP2A6*.

This box summarizes key points contained in the article.

more frequent in the CVI 5-FU group than in the bolus 5-FU group (34 vs 13%). In short-term 5-FU infusion regimens, 5-FU is infused for shorter than 1 week. Currently, the regimens with short-term 5-FU infusion in combination with other anticancer drugs, such as FOLFIRI and FOLFOX, have been widely utilized [9]; in these regimens, however, the effective plasma concentration of 5-FU is sustained for only 24 or 46 h in the 2-week therapeutic cycle, and the anticancer efficiency of 5-FU cannot be exerted efficiently in those regimens although 5-FU is considered as a core drug.

It is difficult to sustain the effective plasma concentration of 5-FU with orally administered 5-FU itself. To enhance the anticancer efficacy of fluoropyrimidines, to reduce the adverse reactions of 5-FU and to overcome problems arising from regimens with long-term or short-term 5-FU infusion, orally administrable fluoropyrimidines have been developed as a masked form (prodrug). Historically, both the academia and pharmaceutical industry in Japan have contributed to the development of oral fluoropyrimidines. Capecitabine has been approved in over 100 countries. On the other hand, S-1, a tegafur (FT)-based oral anticancer prodrug in combination with a dihydropyrimidine dehydrogenase (DPD) inhibitor (5-chloro-2,4-dihydroxypyridine (CDHP)) and an orotate phosphoribosyltransferase (OPRT) inhibitor (potassium oxonate (Oxo)), has been used limitedly only in Japan and some other Asian countries so far. Recently growing evidence on the usefulness of S-1 in preoperative [10,11] and postoperative [12-14] settings has been accumulated. This article reviews the history of 5-FU research, discusses why S-1 is advantageous, summarizes Phase III clinical trials of S-1 and finally provides the alternate-day S-1 administration as a novel regimen that improves the dosing schedule for 5-FU by utilizing its strongly time-dependent mode of action.

2. History of 5-FU research

The development of 5-FU [4] was preceded by important discoveries, for example, the preferred incorporation of uracil into tumor tissues rather than thymine or cytosine (**Figure 1B**) [15] and the antitumor activity of pyrimidine derivatives [16-18]. In the 1950s to 1960s, a series of important discoveries on 5-FU metabolism were reported (**Figure 1C**) [19]. 5-FU is so similar to uracil and thymine in chemical structure that it is recognized by all enzymes involved in uracil metabolism except for one, deoxythymidine monophosphate (dTMP) synthase. 5-FU is converted to fluorouridine monophosphate (FUMP) by OPRT with phosphoribosyl pyrophosphate (PRPP) as a cofactor, and FUMP is further phosphorylated to fluorouridine diphosphate (FUDP), which is either further converted to fluorodeoxyuridine diphosphate (FdUDP) by ribonucleotide reductase, or phosphorylated to the active metabolite fluorouridine triphosphate (FUTP). FdUDP is then either further dephosphorylated to fluorodeoxyuridine monophosphate (FdUMP) or phosphorylated to fluorodeoxyuridine triphosphate (FdUTP). FdUMP binds to dTMP synthase and forms a ternary complex with 5,10-methylene tetrahydrofolate (CH_2THF) (**Figure 1C**) [20]. FdUTP and FdUMP cause DNA damage, while FUTP causes RNA damage [21]; among them, the ternary complex causes the main anticancer activity of 5-FU [22]. Meanwhile, 5-FU is catabolized by DPD into 5-fluoro-5,6-dihydrouracil (FDHU) very rapidly, and further into α-fluoro-β-ureidopropionic acid (FUPA) and α-fluoro-β-alanine (FBAL) (**Figure 1C**) [23]. Approximately 90% of 5-FU in plasma are degraded into FUPA and FBAL by DPD in the liver and are excreted as FBAL in the urine within 24 h, and only 10% of 5-FU are anabolized into fluorinated RNA (F-RNA), fluorinated DNA (F-DNA) and FdUMP [24]. FBAL is further catabolized into fluorinated acetyl-CoA (F-acetyl-CoA) and fluorinated citrate (F-citrate) (**Figure 1C**).

Since the 1970s, the adverse reactions of 5-FU anabolites and catabolites have been investigated energetically, and the overwhelming majority of 5-FU research by Martin *et al.* [25] and other groups demonstrated that incorporation of RNA and impairment of RNA maturation are the main culprits for

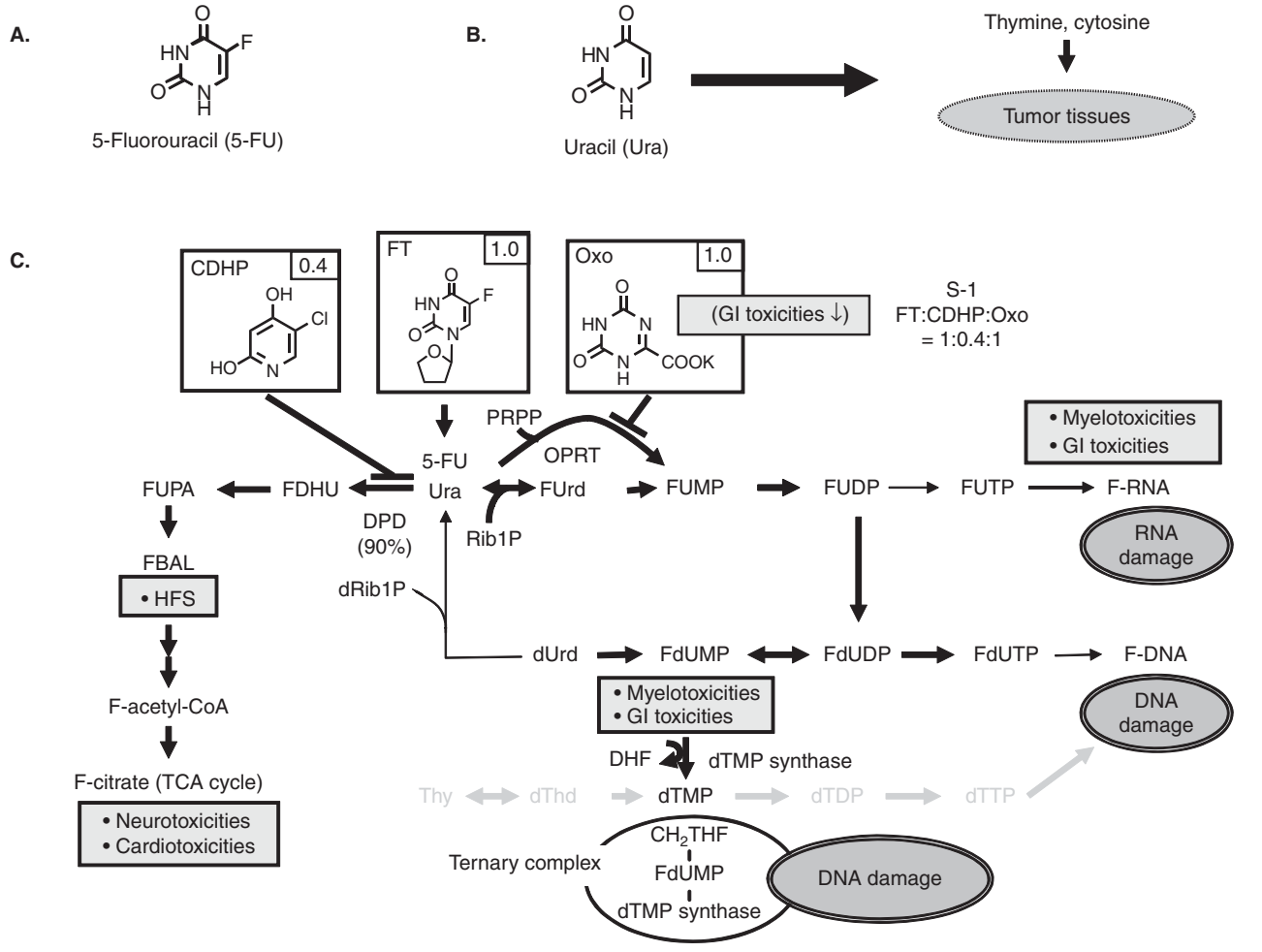

Figure 1. A. A chemical structure of 5-fluorouracil (5-FU). **B.** Preferable incorporation of uracil into tumor tissues. **C.** 5-FU metabolism and S-1. Toxicities are indicated in grey rectangles.

CDHP: 5-chloro-2,4-dihydroxypyridine; CH_2THF: 5,10-methylene tetrahydrofolate; DHF: Dihydrofolate; dRib1P: Deoxyribose-1-phosphate; dTMP: Deoxythymidine monophosphate; dUrd: Deoxyuridine; F-acetyl-CoA: Fluorinated acetyl-CoA; FBAL: α-fluoro-β-alanine; F-citrate: Fluorinated citrate; FDHU: 5-fluoro-5,6-dihydrouracil; F-DNA: Fluorinated DNA; FdUMP: Fluorodeoxyuridine monophosphate; FdUTP: Fluorodeoxyuridine triphosphate; F-RNA: Fluorinated RNA; FT: Ftorafur; FUPA: α-fluoro-β-ureidopropionic acid; FUTP: Fluorouridine triphosphate; GI: Gastrointestinal; Oxo: Potassium oxonate; PRPP: Phosphoribosyl pyrophosphate; Rib1P: Ribose-1-phosphate.

5-FU host toxicity [26]; on the other hand, FdUMP has also been reported to cause myelotoxicities [27] and GI toxicities [28]. HFS is a common adverse event in patients treated with CVI 5-FU or capecitabine, and is caused by FBAL and FDHU [29]. Koenig and Patel found that the neurotoxicities of 5-FU are due to F-citrate that works as an inhibitor of the Krebs' citric acid cycle by blocking aconitase [30]. With open-chest guinea pigs, furthermore, Matsubara *et al.* revealed that the cardiotoxicities of 5-FU are also due to the accumulation of citrate within the myocardium, suggesting a malfunction of the citric acid cycle resulting from the inhibition of aconitase by F-citrate [31]. As Peters *et al.* pointed out in their pharmacokinetic study in 2003 [29], the addition of a DPD inhibitor to fluoropyrimidine treatments can significantly diminish the incidences of HFS by preventing the synthesis of 5-FU catabolites.

3. Why is the oral intake of fluoropyrimidines advantageous?

The implantation of a central venous port is recommended for CVI 5-FU and short-term 5-FU infusion regimens. However, complications associated with port systems, for example, pneumothorax, hemothorax, device disconnection, catheter-related infection and thrombosis, are serious problems for patients [32,33]. Oral administration allows the avoidance of such iatrogenic issues, and the cost–benefit balance has been discussed [34,35]; furthermore, recent studies have revealed that patients prefer oral administration to infusional 5-FU procedures [36,37]. Recently, clinical studies have shown that regimens with oral fluoropyrimidines (uracil-ftorafur (UFT), S-1 and capecitabine) are not inferior to those with

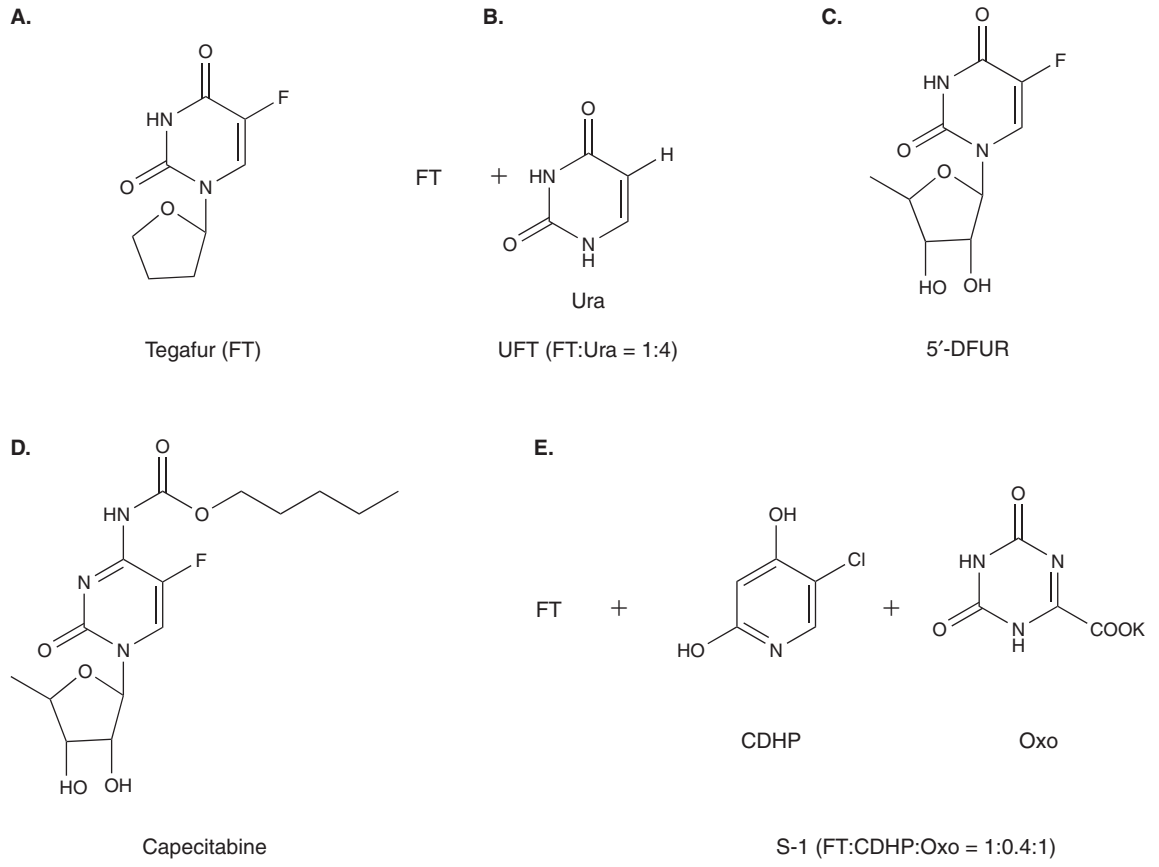

Figure 2. Chemical structures of oral fluoropyrimidines.

short-term [38-43] or bolus [44,45] 5-FU infusion; in some of the studies, OS appeared even better [43]. Considering all of the above, most of the regimens with short-term or bolus 5-FU infusion, which are widely used in the current clinical setting, can be replaced by oral fluoropyrimidine-based regimens.

4. Orally administrable fluoropyrimidines

Oral fluoropyrimidines were developed as a prodrug and some of those were combined with chemical drugs such as DPD inhibitors. There are two lineages of development: from FT and UFT to S-1; and from 5′-deoxy-5-fluorouridine (5′-DFUR) to capecitabine.

1-(2-Tetrahydrofuryl)-5-fluorouracil (e.g., FT-207; **Figure 2A**) was developed as a 5-FU prodrug by Giller *et al.* in the Soviet Union in 1967 [46]. A Phase II clinical study on the intravenous administration of FT showed the unignorable GI toxicities and disturbances of the central nervous system; no further study with FT was suggested in the USA [47]. FT is gradually converted into 5-FU via cytochrome P450 2A6 (CYP2A6) in hepatic microsomes [48]. Utilizing the excellent absorbability of FT and its slight conversion in the GI tract, the orally administrable form of FT was developed in the 1970s by Kimura, Fujii and Taguchi in Japan [49]. However, plasma concentrations of 5-FU after oral administration of FT were still very low.

In 1978, Fujii *et al.* found that uracil prevents growth inhibition which is induced by 5-FU in human normal cells, but not in cancer cells even at 1000 times the concentration of 5-FU [50]. Such a contradictory effect led to the development of UFT (**Figure 2B**), in which FT and uracil were combined at their optimal molecular ratio of 1:4 [51]. The combination of uracil allowed UFT to exhibit more potent antitumor activity than does FT. Nevertheless, UFT failed to sustain the effective plasma concentration of 5-FU for a time as long as CVI 5-FU regimens could provide. These efforts led to the development of S-1.

Cook *et al.* in 1979 [52] and Ishitsuka *et al.* in 1980 [53] reported the development of 5′-DFUR (doxifluridine, furtulon; **Figure 2C**). 5′-DFUR is a 5-FU prodrug and can be promptly activated by both thymidine phosphorylase (dThdPase) and uridine phosphorylase (UrdPase) [53-55]. Next, N(4)-pentyloxycarbonyl-5′-deoxy-5-fluorocytidine (capecitabine; **Figure 2D**) [56] was approved as a next-generation agent succeeding 5′-DFUR. To design the optimized fluoropyrimidine carbamate, a series of N4-alkoxylcarbonyl derivatives were screened for hydrolysis to 5′-deoxy-5-fluorocytidine (5′-DFCR), specifically by carboxylesterase [56]. During the screening process, derivatives

having an N4-alkoxylcarbonyl moiety with a C4-C6 alkyl chain were the most susceptible to human carboxylesterase, which led to the development of capecitabine [57]. Capecitabine passes intact through the gut wall as a prodrug, and is serially converted into 5′-DFCR, 5′-DFUR and finally into 5-FU, through a cascade of enzymes: carboxylesterase, cytidine deaminase and finally dThdPase and UrdPase. In 2003, Peters et al. demonstrated in their pharmacokinetic studies that FBAL formation was low when DPD inhibition was present [29], who also postulated that HFS might be related to FBAL. HFS is a leading cause of capecitabine discontinuation [58]. In fact, Cmax of FBAL after capecitabine administration (5390 ng/ml) is extremely high compared with Cmax of 5-FU (404 ng/ml) [59], and the inhibition of DPD activity is eagerly desired. DPD inhibitors such as RO0094889 [60] were combined with capecitabine in preclinical studies; to date, however, capecitabine has not been used in combination with DPD inhibitors.

5. The concept of S-1

The development of S-1 (**Figures 1C** and **2E**) [61] was accomplished based on the discoveries of two important chemical drugs: CDHP and gimeracil [62] as a DPD inhibitor and Oxo [63] as an OPRT inhibitor (**Figures 1C** and **2E**). Compared with uracil, the DPD-inhibitory activity of CDHP was intensified by 200-fold. On the other hand, with addition of CDHP, long-lasting high plasma concentrations of 5-FU after S-1 administration were predicted to induce severe GI toxicities (**Figure 1C**), and Oxo was discovered to reduce GI toxicities of 5-FU [63]. Granat *et al.* had already attempted to intravenously use Oxo as an anticancer agent; however, intravenously infused Oxo showed insufficient anticancer activity [64]. On the other hand, orally administered Oxo was shown to selectively localize in normal GI tract but not in tumor tissues, and to markedly reduce the GI toxicities of 5-FU without influencing its antitumor effect [63]. With this discovery, dual actions could be clinically expected by adding CDHP and Oxo to FT, that is, effect-enhancing activity with high plasma concentrations of active 5-FU and adverse reaction-reducing activity (**Figure 1C**) [65], and a suitable formulation of S-1, consisting of FT, CDHP and Oxo at a molar ratio of 1:0.4:1 (**Figure 2E**), was finally proposed [61].

In the 1990s, the early Phase II studies of S-1 in Japanese cancer patients were conducted by Hirata *et al.* [66], with 80 mg/m^2/day of S-1 twice daily for 4 weeks followed by 2-week withdrawal, which is currently the standard administration schedule in Japan. In this study, all of the patients showed Cmax of 5-FU to be 60 – 200 ng/ml, which were almost equivalent to or higher than those obtained by CVI 5-FU [66], and other pharmacokinetic parameters were as follows: Tmax, 3.5 ± 1.7 h; $AUC_{(0\text{-}14\ h)}$, 723.9 ± 272.7 ng × h/ml and $T_{1/2}$, 1.9 ± 0.4 h. The pharmacokinetics of orally administered S-1 was almost equivalent to that of CVI 5-FU, and dominant adverse events were hematological toxicities [66]. With addition of CDHP and Oxo, the total daily dose of FT in S-1 was reduced to one-tenth compared with that of oral FT (120 mg/day in S-1, 600 mg/day in UFT and 1200 mg/day in oral FT). On the other hand, initial studies of S-1 in Europe and in the USA were conducted in the early 2000s, with more tight administration schedules, which will be discussed in later sessions.

Compared with other oral fluoropyrimidines, S-1 is considered to have the following advantages. First, in 2008 Yen-Revollo *et al.* reviewed that Cmax of FBAL after S-1 administration is extremely low compared with that after capecitabine administration, concluding that treatments with fluoropyrimidines should include DPD inhibitors as standard therapy [67]. Second, Yamashita *et al.* showed in *in vivo* rat studies that Oxo reduces immunosuppression induced by 5-FU, maintaining normal gut immunity [68]. Third, FT in S-1 is converted into active 5-FU by *CYP2A6*; on the other hand, capecitabine is converted into 5-FU through a cascade of enzymes, and plasma 5-FU concentrations after capecitabine administration can be more affected by DPD; hence, plasma 5-FU concentrations vary less extensively after S-1 administration than after capecitabine administration. Fourth, S-1 can be safely administered to cancer patients with DPD deficiency because DPD is already inactivated by CDHP when S-1 is administered. Since incorporation of 5-FU into RNA causes the 5-FU host toxicity [25], the uridine prodrug triacetyluridine was registered as an orphan drug to protect against 5-FU toxicity, and it was indicated as a rescue when a patient with DPD deficiency would get 5-FU [69]. Fortunately, this is less likely to happen in patients with S-1 administration because the dose of S-1 is determined under DPD inhibition by CDHP.

In Japan, since 1999 S-1 has been approved for gastric cancer, head and neck squamous cell carcinoma, colorectal cancer, non-small cell lung cancer, advanced breast cancer, pancreatic cancer and biliary tract cancer.

6. Phase III clinical trials of S-1

As of 1 December 2011, 44 of the Phase III randomized clinical trials of S-1 have been publicly registered in Asia, Europe and the USA. Among them, 14 studies were conducted in the postoperative adjuvant setting, among which the ACTS-GC study conducted in Japan was published in an article (**Table 1**) [13]. The purpose of the ACTS-GC study was to evaluate the efficacy of S-1 in curatively resected Japanese gastric cancer patients as an adjuvant chemotherapy compared with the surgery-only group. In this study, S-1 was given by the standard regimen in Japan: 4-week administration followed by a 2-week withdrawal with 80 mg/m^2/day in 1-year adjuvant chemotherapy (the S-1 group). Adverse events of grade 3/4 that were relatively common in the S-1 group were anorexia (6.0%), nausea (3.7%) and diarrhea (3.1%). The 3-year OS rate was 80.1% in the S-1 group compared with 70.1% in the surgery-only group, with a hazard ratio

Table 1. Phase III clinical trials of S-1.

Acronym (Country)	Inclusion criteria	Drug	Per day	On days	Duration	No. of patients	Outcome	Ref.
Gastric cancer, adjuvant								
ACTS-GC (Japan)	Stage II/IIIA/IIIB	S-1	80 mg/m^2 *p.o.**	1 – 28	q6wks	529	3 year OS 80.1%	[13]
		Surgery alone				530	70.1% (HR = 0.68, p = 0.003)	
Gastric cancer, advanced								
SPIRITS (Japan)	No prior CT/RT	S-1	80 mg/m^2 *p.o.**	1 – 28	q6wks	150	Median OS 11 mos.	[70]
		S-1 CDDP	80 mg/m^2 *p.o.** 60 mg/m^2	1 – 21 8	q5wks	148	13 mos. (HR = 0.77, p = 0.04)	
JCOG9912 (Japan)	No prior CT	S-1	80 mg/m^2 *p.o.**	1 – 28	q6wks	234	Median OS 11.4 mos.	[71]
		Infusional 5-FU (5 days)	800 mg/m^2	1 – 5	q4wks	234	10.8 mos. (HR = 0.83, p = 0.0005 for non-inferiority)	
		CPT-11 CDDP	70 mg/m^2 80 mg/m^2	1,15 1	q4wks ‡	236	12.3 mos.	
FLAGS (24 non-Asian countries)	No prior CT, includes GEJC	S-1 CDDP	50 mg/m^2 *p.o.* 75 mg/m^2	1 – 21 1	q4wks	527	Median OS 8.6 mos.	[42]
		Infusional 5-FU (5 days) CDDP	1000 mg/m^2 100 mg/m^2	1 – 5 1	q4wks	526	7.9 mos. (HR = 0.92, p = 0.20)	
TOP-002 (Japan)	No prior CT/RT	S-1	80 mg/m^2 *p.o.**	1 – 28	q6wks	162	Median OS 10.5 mos.	[72]
		S-1 CPT-11	80 mg/m^2 *p.o.** 80 mg/m^2	1 – 21 1,15	q5wks	164	12.8 mos. (HR = 0.856, p = 0.233)	
Colorectal cancer, advanced								
FIRIS (Japan)	Second-line CT	S-1 CPT-11	80 mg/m^2 *p.o.** 125 mg/m^2	1 – 14 1,15	q4wks	213	Median PFS 5.8 mos.	[43]
		Folinic acid CPT-11 Bolus 5-FU Infusional 5-FU (46 hrs)	200 mg/m^2 150 mg/m^2 400 mg/m^2 2400 mg/m^2	1,15 1,15 1,15 1 – 2,15 – 16	q4wks	213	5.1 mos. (HR = 1.007, p = 0.039 for non-inferiority)	

*S-1 was orally administered twice daily with the dose of 40 mg for patients with BSA < 1.25 m^2; 50 mg for patients with BSA 1.25 to 1.5 m^2 and 60 mg for patients with BSA ≥ 1.5 m^2.

‡After six therapeutic cycles, the same dose of CPT-11 alone was continued every 2 weeks.

BSA: Body surface area; CDDP: Cisplatin; CPT-11: Irinotecan; CT: Chemotherapy; GEJC: Gastroesophageal junction cancer; HR: Hazard ratio; mos.: Months; OS: Overall survival; *p.o.*: Oral administration; PFS: Progression-free survival; RT: Radiotherapy.

(HR) of 0.68 (95% confidence interval (CI) 0.52 to 0.87, p = 0.003) [13]; in 2007 S-1 gained a position as the standard agent for adjuvant chemotherapy of gastric cancer in Japan.

Among 28 of the Phase III studies of S-1 in advanced cancers, furthermore, the articles on four trials in advanced gastric cancer (SPIRITS [70], JCOG9912 [71], FLAGS [42] and TOP-022 [72]) and on one trial in advanced colorectal cancer (FIRIS) [43] were published (**Table 1**). Among them, only the FLAGS study was conducted outside Japan.

In the SPIRITS study conducted in Japan [70], S-1 monotherapy and S-1/cisplatin therapy were compared in advanced gastric cancer patients. S-1 was administered with 80 mg/m^2/day for 4 weeks as monotherapy or for 3 weeks in combination with cisplatin (**Table 1**), and the median OS in patients assigned to the S-1/cisplatin group was significantly longer than that assigned to the S-1 alone group (13 and 11 months, respectively; HR: 0.77; 95% CI 0.61 to 0.98; p = 0.04). Common adverse events in the S-1 group were neutropenia, pigmentation and leucopenia. Next, in the JCOG9912 study conducted in Japan [71], the median OS of patients treated with S-1 (80 mg/m^2/day) for 4 weeks followed by 2-week withdrawal (11.4 months) was not inferior to that of patients treated with short-term 5-FU infusion for 5 days in 4 weeks as one therapeutic cycle (10.8 months, p = 0.0005 for non-inferiority) [71]. Frequencies of grade 3/4 adverse events in patients assigned to S-1 were similar to those seen in patients with short-term 5-FU infusion except for a higher rate of diarrhea in the S-1 group. Next, the purpose of the FIRIS study conducted in Japan was to compare the IRIS study (S-1 plus irinotecan) with the FOLFIRI study in advanced colorectal cancer [43]; progression-free survival (PFS) in the IRIS study was not inferior to that in the FOLFIRI study (p = 0.039) and was even better (5.8 and 5.1 months, respectively), suggesting IRIS to be an additional therapeutic option.

On the other hand, the FLAGS study was conducted in 24 non-Asian countries with the western dose of S-1 (50 mg/m^2/day) for 3 weeks followed by 1-week rest (**Table 1**) [42]. In the FLAGS study, the combination of the western dose of S-1 and cisplatin showed a significantly improved profile of safety, especially on grade 3/4 neutropenia, complicated neutropenia, stomatitis, hypokalemia and treatment-related deaths, despite not presenting prolonged OS [42]. Based on the promising results from the FLAGS study, the European Commission has granted in 2011 the marketing authorization of S-1 for advanced gastric cancer in combination with cisplatin. In addition, following a Phase II study of S-1 in metastatic pancreatic cancer patients conducted by the CESAR study group [73], a Phase III study was suggested to further confirm the efficacy of S-1 in Europe, with 60 mg/m^2/day for 2 weeks, repeated every 3 weeks.

7. Ethnic difference in pharmacokinetics of S-1

Currently, S-1 administration with 80 mg/m^2/day for 4 weeks followed by 2-week withdrawal is the standard administration schedule in Japan. On the other hand, in initial Phase I studies of S-1 conducted in Europe and in the USA in the early 2000s [74-76], S-1 was administered for 4 weeks followed by 1-week withdrawal. With such a tight administration schedule, the recommended dose was determined to be 50 mg/m^2/day [74], 60 mg/m^2/day [75] or even 80 mg/m^2/day [76], dose which as that in Japanese studies. With such administration schedules and doses in Europe and in the USA, patients treated with S-1 showed more diarrhea and other GI toxicities than patients studied in Japan. After that time, the administration doses and schedules were re-evaluated, but Caucasians still had more GI toxicities than Japanese. In the 1990s, one of the clear ethnic differences had been recognized as being *CYP2A6* which catalyzes FT conversion to 5-FU [48]. In 2003, Peters *et al.* reported the pharmacokinetic study of S-1 in Caucasians [29], and this study as well as the Phase I studies at that time [74-76] revealed marked differences in pharmacokinetics of not only 5-FU, but also of FT, CDHP and Oxo between Caucasians and Japanese. In 2011, Chuah *et al.* reported the prospectively randomized two-arm study to compare the pharmacokinetics and pharmacodynamics of S-1 in East Asian and Caucasian cancer patients [77], in both of which S-1 was given orally at 60 mg/m^2/day for 2 weeks with 1-week withdrawal. In this study, the dose normalized $AUC_{(0\text{-}48\ h)}$ for FT (p = 0.05) and that for CDHP (p = 0.036) were higher in East Asians; conversely, $AUC_{(0\text{-}48\ h)}$ of FBAL was higher in Caucasians (p = 0.044), and grade 3/4 GI toxicities were more common in Caucasians than in Asians (21 vs 0%) [77]. In this study, however, Oxo had similar pharmacokinetics in both ethnic groups and therefore did not explain differences in GI adverse events. On the other hand, studies conducted in Europe by Peters *et al.* [78] and by Scheulen *et al.* [79] showed that oral bioavailability of Oxo is erroneously reduced by food intake rather than in fast condition, which has to be evaluated to analyze pharmacokinetics of S-1.

8. Alternate-day S-1 administration

Although the oral administration of fluoropyrimidines has advantages, the emergence of GI toxicities is inevitable. Grade 1 diarrhea means 'increase of less than four stools per day over baseline', and grade 1 vomiting means 'one to two episodes in 24 h' in the CTCAE version 4.0. Although Grade 1/2 GI toxicities have not been discussed to cause 5-FU disconnection, patients have difficulties to continue the oral administration of anticancer agents if GI toxicities exceed grade 1; therefore, patients should be free of GI discomfort to continue oral administration, which allows daily eating, free outing and work. In Japan, S-1 administration in clinical settings was started with the daily S-1 regimen at 4-week administration and 2-week withdrawal. In the ACTS-GC study [13], the incidences of diarrhea and vomiting with the daily S-1 regimen were 59.8 and 22.6%, respectively, which means that almost 70% of patients had difficulty continuing the 6-month

administration of S-1. On the other hand, initial Phase I studies of S-1 conducted in Europe and in the USA were started with more tight administration schedules such as 4 weeks administration followed by 1-week withdrawal [74-76]. To reduce GI toxicities of patients, 2- or 3-week administration of S-1 followed by 1-week rest has been proposed as an alternate schedule [42,73,78,79]; however, in these schedules 5-FU is not administered for as long as 1 week, during which the anticancer efficacy of 5-FU cannot be exerted.

In S-1, Oxo can reduce GI toxicities but does not reduce myelotoxicity. To minimize GI toxicities as well as myelotoxicities without reducing the anticancer efficacy of 5-FU, the alternate-day S-1 administration has been proposed (**Figure 3**), which was designed based on antecedent studies on cell division. In 1963 and later, the results by Lipkin *et al.* [80] and Clarkson *et al.* [81] showed differences in the cell cycle between normal epithelial cells of GI tract and disseminated cancer cells from stomach adenocarcinoma and other malignancies (**Figure 3**). The generation time (T_G) of normal GI and hematopoietic cells lasts for as very shortly as 0.5 – 0.7 days, which is shorter than that of cancer cells (4 – 5 days); the duration of the S-phase, during which 5-FU works predominantly, is 9 – 14 h in normal cells and is again shorter than that in cancer cells (17 – 60 h). By taking advantage of these differences in the cell cycle, Terashima *et al.* reported the usefulness of the alternate-day intravenous infusion of 5-FU [82], and another administration schedule utilizing this advantage is the alternate-day S-1 administration in which S-1 is administered on every other day (**Figure 3**). In advanced gastric cancer patients, Arai *et al.* compared two administration schedules of S-1: the daily S-1 regimen and alternate-day S-1 administration. While S-1 administration was continued under the two schedules, the plasma 5-FU concentrations were measured at 0, 2, 4 and 6 h after S-1 intake (**Figure 4A**). In this study, the trough level of 5-FU before S-1 administration in the alternate-day S-1 administration group was significantly low (2.1 ng/ml) compared with that in the daily S-1 regimen group (10.4 ng/ml) although the plasma 5-FU concentration peaked at the effective level in both groups (**Figure 4A**); this led to the extremely low incidence of non-hematologic adverse events in the alternate-day S-1 administration group [83]. In addition, while 5-FU level in plasma declines on Tuesday, Thursday and Saturday (**Figure 3**), 5-FU level in tumors is supposed to be maintained at certain levels, which is indicated by previous *in vivo* studies using rats [49,61]. Next, in *in vivo* studies using MKN28-bearing nude mice (**Figure 4B**), atrophic changes and inflammatory cell infiltration were noted in the daily S-1 regimen group, but the alternate-day S-1 administration markedly reduced the GI toxicities of 5-FU along with the minimal atrophic changes of the GI mucosa [84]. In a retrospective study of unresectable gastric cancer patients by Sakuma *et al.* [85], the median OS of patients undergoing the alternate-day S-1 regimen was 338 days, which was equivalent to that with the daily S-1 regimen in the SPIRITS study (11 months, **Table 1**) in advanced gastric cancer [70]. In this study, the incidence of non-hematologic toxicities of the alternate-day S-1 administration group dramatically decreased compared with that of the daily S-1 regimen group (**Figure 5**), enabling patients of the alternate-day administration group to continue the oral administration of S-1 for 6 – 12 months without reducing the dose intensity of 5-FU [85]. To further confirm the efficacy of the alternate-day S-1 administration, two prospective, randomized Phase II studies of advanced cancer patients are ongoing in Japan. In one of the studies, 48 patients with unresectable pancreatic cancer were registered and the overall incidence of GI toxicities with the alternate-day S-1 administration did not exceed 10%, and almost all of patients were able to continue the standard dose of S-1. In addition, in another Phase II study as an adjuvant setting, 70 curatively resected gastric cancer patients were registered, and the alternate-day S-1 administration group revealed a higher treatment accomplishment rate and higher dose intensity than the group of the daily S-1 regimen (the ESMO 13th World Congress on Gastrointestinal Cancer in 2011, abstract No. 6521). The alternate-day S-1 administration may be beneficial to Caucasians who have more severe GI toxicities than Asians although the reasons for different profiles of adverse events between Caucasians and Asians have to be more evaluated. Under this regimen, the optimized doses of S-1 in Caucasians and Asians will be re-evaluated.

9. Conclusion

In this review, we proposed that most regimens with short-term or bolus 5-FU infusion, which have been widely used in the current clinical settings, can be replaced by oral fluoropyrimidines, especially by the alternate-day S-1 administration. Recently, the pharmacogenomic studies of *CYP2A6* [86,87], *OPRT* [88], *DPD* [89,90] and other enzymes have been reported. The accumulated results from such pharmacogenomics studies and their utilization shall enable the optimized administration of oral fluoropyrimidines for each of cancer patients. We believe that information in this review may be greatly beneficial to scientists in the pharmaceutical industry, academic pharmaceutical scientists and clinicians around the world, and can be utilized for individual cancer patients as well.

10. Expert opinion

Currently, a large number of small molecules and monoclonal antibodies for targeted therapies are under development. Among them, a limited number of drugs have been available to date that exert their anticancer efficacy as core drugs. By contrast, 5-FU has been and will further continue to be the standard drug for GI and other malignancies. Late effects of anticancer agents in cancer survivors, such as cardiac or pulmonary dysfunction, growth disorder and gonadal dysgenesis, are problems to be overcome. For this meaning,

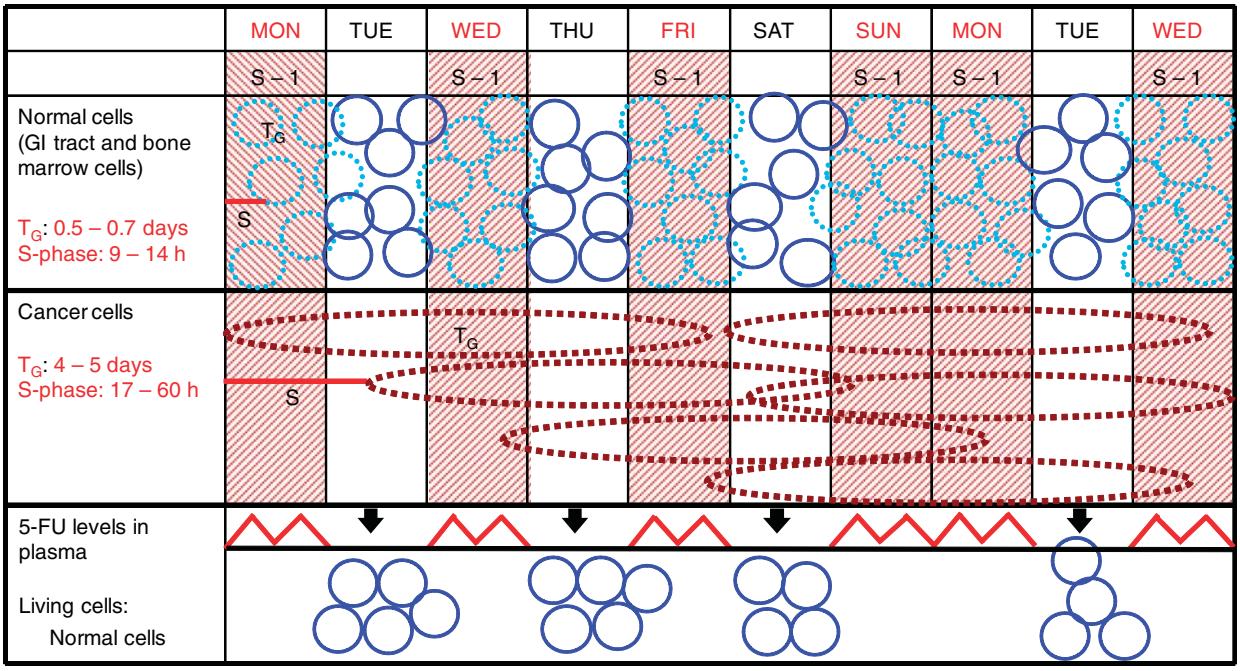

Figure 3. The rationale for the alternative-day S-1 administration. The generation time (T_G) of normal GI and hematopoietic cells lasts for as very shortly as 0.5 – 0.7 days, and the duration of the S-phase is 9 – 14 h, both of which are shorter than those in cancer cells [80,81]. By taking advantage of these differences, in the alternate-day S-1 administration, S-1 is administered on Monday, Wednesday, Friday and Sunday twice daily, but not administered on other days. While 5-FU level in plasma declines on Tuesday, Thursday and Saturday, 5-FU level in tumors is supposed to be maintained at certain levels, which is indicated by previous *in vivo* studies using rats [49,61].

fluoropyrimidines can be safely used and are possibly applied to childhood malignancies as well. Since the 1970s, Japan has contributed to the development of oral fluoropyrimidines (UFT, 5′-DFUR, S-1, capecitabine and others). Each of the oral fluoropyrimidine prodrugs has its own properties and undergoes diverse metabolic changes to be converted into the active form 5-FU, and 5-FU is further anabolized or catabolized. Since the activities of all enzymes involved in the conversion and metabolism of 5-FU vary interindividually and interethnically, information on the pharmacokinetics of respective oral fluoropyrimidines should be systematically arranged. *CYP2A6* is involved in the conversion of FT into 5-FU. The Japanese population show very low or undetectable levels of *CYP2A6*; however, Caucasians have significant *CYP2A6* levels, and most recently the pharmacogenomic studies of *CYP2A6*, *OPRT* and other genes have been accumulated as well. The clearance of FT in patients with advanced cancer depends on variant alleles at the polymorphic regions of the *CYP2A6* gene. The association of genetic polymorphism of the *OPRT* gene with GI toxicities such as diarrhea has been discussed. DPD deficiency is more common in African-Americans than in Caucasians, and not only genomic deletions affecting the *DPD* gene but also its deep intronic mutations affecting pre-mRNA splicing can cause severe 5-FU-associated toxicities. The accumulated results from pharmacogenomics studies and their utilization enable us to further optimize the administration of oral fluoropyrimidines for each of cancer patients, and such information with pharmacogenomics has to be correlated to pharmacokinetic data and clinical information from cancer patients. Capecitabine has been approved in over 100 countries; on the other hand, S-1 has been used limitedly only in Japan and some other Asian countries so far. In Europe, the marketing authorization of S-1 was granted in 2011; quite recently, growing evidence on the usefulness of S-1 has been accumulated. The alternate-day S-1 administration was designed based on antecedent studies on cell division in the 1960s and the schedule can reduce the GI toxicities and myelotoxicities of 5-FU without reducing its anticancer efficacy, enabling patients to continue the oral administration for 6 – 12 months. Replacement of regimens using infusional 5-FU and other oral fluoropyrimidines with the alternate-day S-1 administration allows the latter to be used efficiently. Furthermore, the alternate-day S-1 administration may give great benefits to Caucasians who experience more severe GI toxicity for FT due to their high activity of *CYP2A6*. The information in this review may be greatly beneficial to scientists in the pharmaceutical industry, pharmacologists and clinical oncologists and toxicologists, and can be utilized for each of cancer patients. To maximally utilize S-1 and other

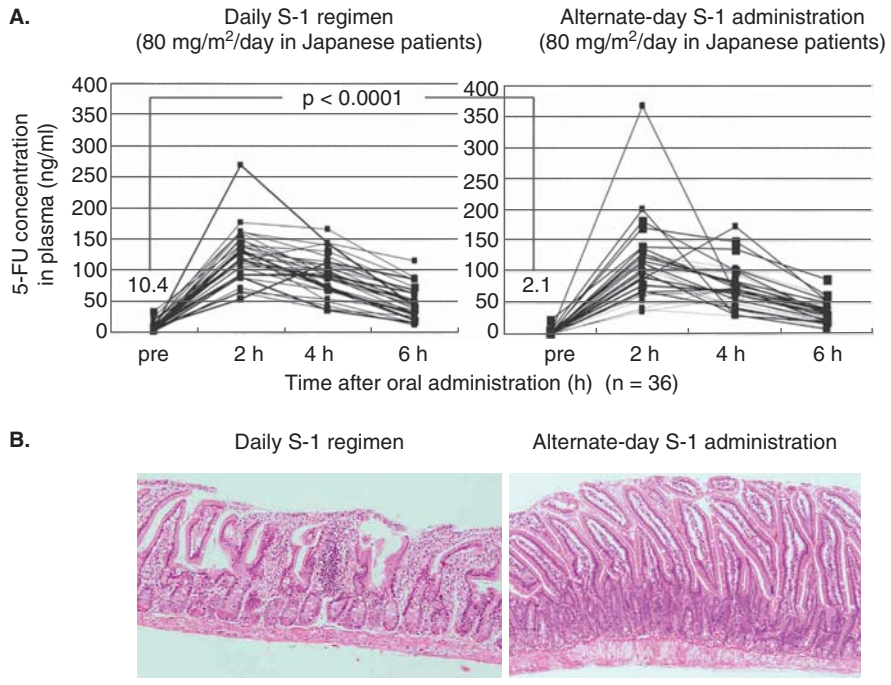

Figure 4. A. Time-dependent changes of plasma 5-FU levels in S-1 administration. The trough levels of 5-FU in the alternate-day S-1 administration group were significantly low (2.1 ng/ml) compared with those in the daily S-1 regimen group (10.4 ng/ml). **B. The intestinal mucosa of MKN28-bearing nude mice after S-1 administration.** The atrophic changes and inflammatory cell infiltration were minimal in the alternate-day S-1 administration.

Figure 4A Reproduced with permission from Arai *et al.* [83].

Figure 4B Reproduced with permission from Arai *et al.* [84].

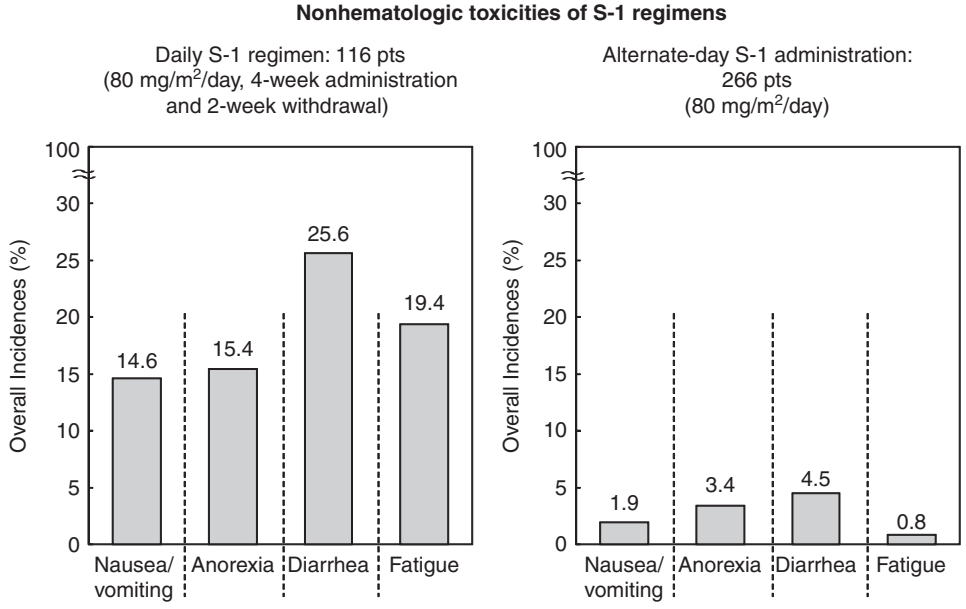

Figure 5. Overall incidences of non-hematologic toxicities in patients with advanced gastric cancer. The incidence of non-hematologic toxicities after the alternate-day S-1 administration decreased dramatically compared with that in the daily S-1 regimen. In both groups, S-1 was administered with 80 mg/m^2/day.

Reproduced with permission from Sakuma *et al.* [85].

fluoropyrimidines, it is important to elucidate the molecular backgrounds in cancer patients; this will require the collaboration of clinicians, researchers dedicated in preclinical research and molecular biologists.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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