The modulated oral fluoropyrimidine prodrug S-1, and its use in gastrointestinal cancer and other solid tumors

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The fluoropyrimidine anticancer agent 5-fluorouracil (5-FU) is active in a wide range of solid tumors, particularly gastric, colorectal, and head and neck cancers. Whilst infusional 5-FU is associated with higher response rates and a favorable safety profile as compared to the classical i.v. bolus administration, prolonged infusions can be inconvenient for the patients and catheter-related problems are common complications. An oral 5-FU formulation would allow for sustained 5-FU plasma concentrations, mimicking the pharmacokinetics (PK) of a continuous infusion with the addition of convenience of administration. The oral administration of 5-FU itself is not feasible due to the high activity of dihydropyrimidine dehydrogenase in the gut wall, which causes rapid metabolism of the drug, and results in decreased and erratic absorption of 5-FU and non-linear PK. To bypass this problem, oral fluoropyrimidine derivatives were developed either in the form of 5-FU prodrugs (i.e. tegafur, doxifluridine or capecitabine), or as enzyme inhibitors (i.e. eniluracil) administered with 5-FU, or as both prodrugs and enzyme inhibitors (i.e. S-1, UFT or BOF-A2). This review will focus on the oral fluoropyrimidine S-1, which consists of the 5-FU prodrug tegafur (ftorafur, FT) and two enzyme inhibitors, i.e. CDHP (5-chloro-2,4-dihydroxypyridine) and OXO (potassium oxonate), in a molar ratio of 1(FT):0.4 (CDHP):1(OXO). Phase II trials have demonstrated that S-1, as a single agent, is active for the treatment of gastric, colorectal, head and neck, breast, non-small cell lung, and pancreatic cancers. Phase III trials are currently underway in gastric cancer and these results are awaited to confirm the phase II findings. Furthermore, the combination of S-1 with cisplatin (CDDP), irinotecan or docetaxel for the treatment of gastric cancer and with CDDP for non-small cell and pancreatic cancer is feasible and active. The activity observed with S-1 in the phase II studies is at least equivalent, if not better, than continuous i.v. and bolus 5-FU and the other oral fluoropyrimidines. Thus, we may finally be seeing the realization of oral treatments for the management of various solid tumors and could be on the brink of a new approach to treatment strategies.

Anti-Cancer Drugs 2004, **15**:85–106

Keywords: biomodulation, oral fluoropyrimidine, S-1, tegafur, TS-1

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Received 16 September 2003 **Revised form accepted** 26 October 2003

Introduction

For decades, 5-fluorouracil (5-FU) has served as an essential part of chemotherapy (CT) regimens for various solid tumors, including gastric, colorectal, pancreatic, breast, and head and neck cancers [1,2]. However, drawbacks of 5-FU include its relative toxicity (myelosuppression and gastrointestinal disorders), short half-life ($t_{1/2}$) in plasma, low bioavailability due to degradation by dihydropyrimidine dehydrogenase (DPD) in the catabolic pathway and 5-FU resistance of many tumors [2,6]. In efforts to improve the efficacy and tolerability of 5-FU, schedule modifications (continuous or prolonged infusion) and biomodulation (addition of leucovorin) were introduced [3].

The problem of the low $t_{1/2}$ of 5-FU (5–20 min) could be overcome by continuous infusion of 5-FU, utilizing portable infusion pumps which allow prolonged cell exposure to the drug [2,7]. As expected, this prolonged exposure results in higher clinical activity [8–10]. A 1998 meta-analysis, comparing continuous infusion 5-FU to bolus 5-FU in patients with colorectal cancer, confirmed a higher response rate (RR) with continuous infusion (22 versus 14%); however, median survival time was similar (11.3 months with continuous infusion versus 12.1 months with bolus treatment) [11]. With regard to toxicity, the continuous infusion also appeared to offer some advantages. The principal toxicities with bolus 5-FU include myelosuppression, oral mucositis and gastrointestinal disturbances (diarrhea, nausea, vomiting) [2,13]. For continuous infusion, principal adverse events include hand–foot syndrome (palmar–plantar erythrodysesthesia, HFS) and gastrointestinal toxicity (mainly diarrhea); however, continuous infusion caused fewer hematologic and gastrointestinal toxicities [12,13].

Despite the improved RR and lower incidence of myelosuppression observed with continuous infusion

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5-FU, this method of administration is costly, inconvenient to the patient and may be associated with venous thrombosis or infection around the catheter [2,6,14,15]. As 5-FU is a small molecule, it lends itself to an oral formulation and good absorption and bioavailability. An oral formulation would have offered an interesting alternative to the i.v. administration of 5-FU, due to the potential convenience and quality of life (QoL) advantages, the ability of mimicking the pharmacokinetics (PK) of continuous infusion, and cost benefits [16]. However, the use of oral 5-FU by itself was not feasible due to its erratic absorption and non-linear PK resulting in marked intra- and inter-patient variability [5,6,17]. The variability in plasma levels may mainly be due to the poor absorption related to the high activity of DPD in the gut wall and the liver, leading to rapid metabolism of 5-FU [6,18]. Intra-patient variability may be associated with the circadian rhythm of DPD activity throughout the day, influencing the catabolism of 5-FU [6,19]. Variations in the elimination of 5-FU may cause inter-patient variability and this might be related to genetic polymorphisms in DPD [6,20,21].

Several options were investigated in attempts to achieve oral formulations of fluoropyrimidines, which would be at least as active as continuous infusion 5-FU, with less toxicity, improved QoL and cost efficiency. Three potential ways to increase the amount of circulating 5-FU included: (i) use of 5-FU analogs/prodrugs, (ii) use of 5-FU and an enzyme inhibitor (i.e. DPD inhibitor), and (iii) use of 5-FU prodrugs in combination with a DPD inhibitor [5,6,19].

This article will review these groups of oral formulations of fluoropyrimidines, with the focus being on S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan).

Mechanism of action

5-FU was synthesized in order to target the enhanced utilization of uracil as the precursor of RNA and DNA pyrimidines in cancer cells [22,23]. It has a fluorine atom substituted in the place of the hydrogen at the carbon-5 position on the pyrimidine ring [22,23]. 5-FU enters the cell through the facilitated uracil transport mechanism [22], and it is metabolized and anabolized by the same enzymes as uracil [2,22,23,24]. There are two routes of metabolism of 5-FU once it has passed into the cell, i.e. the anabolic route (which results in the active metabolites, allowing the fluoropyrimidines to exert their therapeutic effect) and the dominant catabolic route (leading to inactive metabolites and the elimination of the drug). These routes are in competition with each other [2,22].

In the anabolic process, there are three key active metabolites (Fig. 1) [2,22,23]:

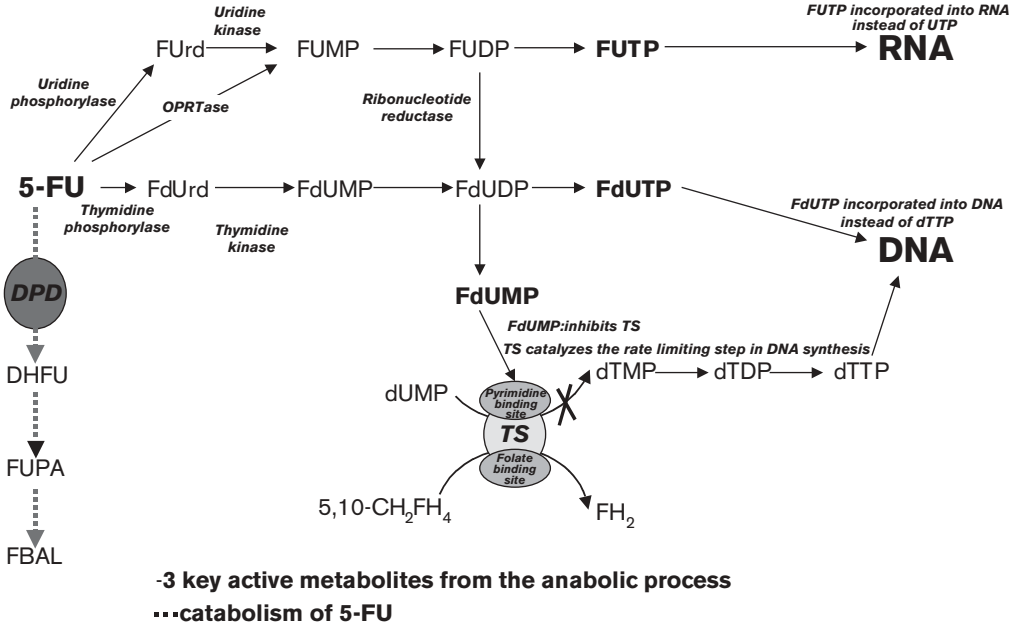
(i) 5-Fluoro-2′-deoxyuridine-5′-monophosphate (FdUMP) which inhibits TS, which catalyzes the rate-limiting step in DNA synthesis.
(ii) 5-Fluorouridine-5′-triphosphate (FUTP), which can be incorporated into RNA instead of uridine-5′-triphosphate (UTP), causing alteration of its processing and functioning.
(iii) 5-Fluoro-2′-deoxyuridine-5′-triphosphate (FdUTP), or deoxyuridine-5′-triphosphate (dUTP), which may be incorporated into DNA instead of deoxythymidine triphosphate (dTTP), which is the normal substrate of DNA polymerase.

Under normal conditions, the activity of TS occurs in two-stages. In the first stage, dUMP binds to a receptor site which induces a configurational change and opens an adjacent binding site for *N*-5,10-methylene-tetrahydrofolate (5,10-CH_2FH_4) [2,3,23,24]. The folate's one carbon group is then transferred to the uridine ring, producing deoxythymidine-5′-monophosphate (dTMP) and dihydrofolate [2,3,23,24]. dTMP is then phosphorylated to deoxythymidine-5′-diphosphate (dTDP) and -triphosphate (dTTP). dTTP is one of the nucleotide bases for DNA synthesis (Fig. 1). However, with 5-FU and the subsequent formation of FdUMP, FdUMP forms a ternary covalent complex with TS and thus inhibits dUMP binding with TS which in turn inhibits the transfer of a methyl group from the carbon-5 of dUMP to form dTMP, resulting in the decreased availability of dTTP for DNA replication and repair (Fig. 1) [2,22,24]. It is difficult for dUMP to compete with the FdUMP–TS complex because the fluorine atom in the C_5 position of 5-FdUMP is more tightly bound than the hydrogen atom on dUMP [2,24].

Thus, the cytotoxic activity of 5-FU is exerted through the suppression of the synthesis of DNA and through the abnormal metabolism of RNA [24]. Some studies suggest that cell death is due primarily to the TS-directed mechanism occurring with prolonged exposure to 5-FU, whilst cell death via a RNA-mediated process mainly occurs with bolus 5-FU administration [2,25–27].

DPD is the rate-limiting enzyme in the catabolism of 5-FU and is responsible for about 85% of the degradation of 5-FU (Fig. 1) [2,22,28,29]. The first step in this degradation process occurs rapidly; with DPD converting 5-FU to 5,6-dihydro-5-fluorouracil (DHFU). In the catabolic pathway DHFU is then broken down further to yield α-fluoro-β-ureidopropionic acid (FUPA), eventually leading to the formation of α-fluoro-β-alanine (FBAL) [2,22,28,29]. This initial stage of the catabolic pathway leaves only a small amount of 5-FU available for anabolism, required for the therapeutic effect.

Fig. 1



Intracellular metabolism and mechanism of action of 5-FU (adapted from [22]). 5-FU=5-fluorouracil; FUrd=5-fluorouridine; FUMP=5-fluorouridine-5′-monophosphate; FUDP=5-fluorouridine-5′-diphosphate; FUTP=5-fluorouridine-5′-triphosphate; FdUrd=5-fluoro-2′-deoxyuridine; FdUMP=5-fluoro-2′-deoxyuridine-5′-monophosphate; FdUDP=5-fluoro-2′-deoxyuridine-5′-diphosphate; FdUTP=5-fluoro-2′-deoxyuridine-5′-triphosphate; dUMP=2′-deoxyuridine-5′-monophosphate; dTMP=deoxythymidine-5′-monophosphate; dTDP=deoxythymidine-5′-diphosphate; dTTP=deoxythymidine-5′-triphosphate. TS=thymidylate synthase. 5,10-CH_2FH_4=*N*-5,10-methylene-tetrahydrofolate; FH_2=dihydrofolate. DPD=dihydropyrimidine dehydrogenase. DHFU=5,6-dihydro-5-fluorouracil; FUPA=α-fluoro-β-ureidopropionic acid; FBAL=α-fluoro-β-alanine.

Thus, factors that effect the activity of 5-FU include the:

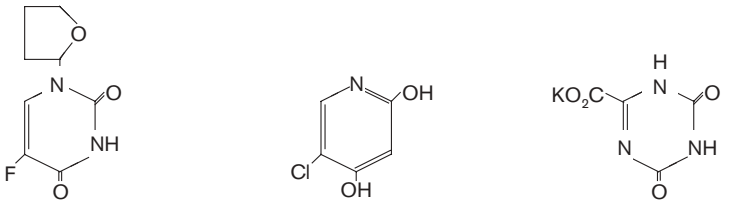
- Activity of the catabolic enzyme DPD
- Amount of TS expression
- Activity of the anabolic enzymes
- Availability of 5-FU activation cofactors [i.e. 5′-phosphoribosyl-1-pyrophosphate (PRPP)]
- Availability of intracellular reduced folate and endogenous dUMP
- Amount of 5-FUTP incorporated into RNA and 5-FdUTP into DNA [2,22,23,27]

The ability to influence these factors would enhance the activity and, in some cases, increase the level of circulating 5-FU. Additionally, by altering some of these factors, oral formulations would also be possible. As mentioned previously, ways in which some of these factors can be influenced is by the use of a prodrug, or an enzyme inhibitor (i.e. DPD inhibitor), or the combination of both a prodrug and enzyme inhibitor [5,6,19]. A prodrug could include a drug that is not a substrate for DPD degradation in the gastrointestinal mucosa and/or a drug that must undergo intracellular activation (either within the liver or tumor itself) by one or more enzyme systems to allow the release of 5-FU [2,5,6].

S-1, developed in Japan in 1993, is one of the newer oral fluoropyrimidine drugs, and consists of a combination of a prodrug and two enzyme inhibitors, or biochemical modulators [2,5,6,28–33]. The 5-FU prodrug of S-1 is tegafur [FT; ftorafur, 1-(2-tetrahydrofuryl)-5-fluorouracil] and the two enzyme inhibitors are 5-chloro-2,4-dihydroxypyridine (CDHP; gimeracil) and potassium oxonate (OXO; oteracil) (Fig. 2) [2,5,6,28–33]. The molar ratio of the three constituents of this combination is 1 (FT):0.4 (CDHP):1 (OXO) (Fig. 2) [24,28–30,34].

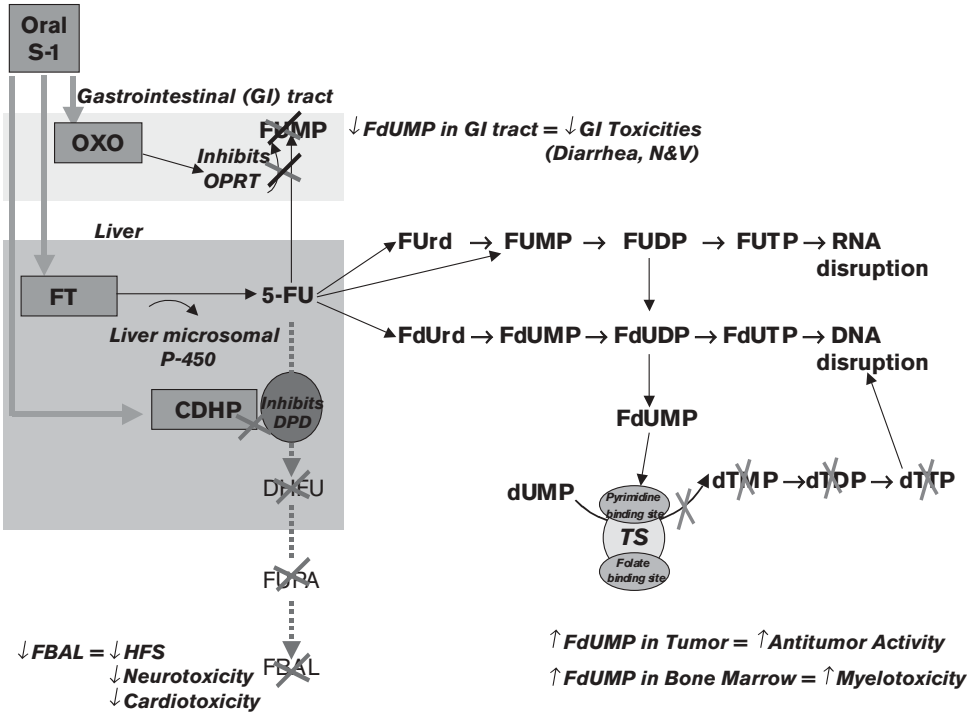
FT is absorbed in the small intestine, and shows good bioavailability and sustained release. Mainly through the liver microsomal P-450 metabolizing enzyme system, FT is converted to 5-FU (Fig. 3) [28,35]. CDHP is a pyrimidine derivative and a reversible competitive inhibitor of DPD (Fig. 3) [28,36]. CDHP is about 180 times more potent than uracil in inhibiting DPD, thus allowing greater concentrations of 5-FU to go through the anabolic pathway, producing the active metabolites which exert their effects on DNA and RNA [28,36]. By combining CDHP with FT, higher concentrations of 5-FU can be retained in the plasma for longer periods of time [28,38]. An *in vitro* study demonstrated that CDHP inhibited 5-FU degradation in human tumor cells, which

Fig. 2



Chemical structure of the components of S-1 [24,29,30,31]. FT=1-(2-tetrahydrofuryl)-5-fluorouracil (tegafur). CDHP=5-chloro-2,4-dihydroxypyridine (gimeracil). OXO=monopotassium 1,2,3,4-tetrahydro-2,4-dioxo-1,3,5-triazine-6-carboxilate (oteracil potassium).

Fig. 3



Mechanism of action of the components of S-1 [24,28–30,31,33]. FT=ftorafur, tegafur. OPRT=orotate phosphoribosyl transferase; further abbreviations, see Figure 1.

suggested that it also exerted DPD inhibition in the tumor as well as in the liver [28]. Furthermore, the inhibition of DPD leads to a reduced amount of FBAL formation, which may result in reduced toxicities such as neurotoxicity [28]. The co-administration of OXO in the S-1 formulation allows for the selective inhibition of the catalytic enzyme orotate phosphoribosyl transferase (OPRT) in the gastrointestinal mucosal cells, which inhibits the phosphorylation of 5-FU to FUMP (and thus decreases the drug incorporation into RNA), this in turn decreases the incidence of gastrointestinal toxicity (Fig. 3) [28,30,39,40]. The selectivity of OXO's inhibition of OPRT in the gastrointestinal tract was demonstrated in the animal study by Shirasaka *et al.*, which showed the

formation of FUMP and incorporation of 5-FU into RNA in the small intestine decreased by about 70%, whereas in bone marrow and tumor regions the output of FUMP decreased only by about 0–20% [30,39]. Possibly this can be explained by the tendency for OXO to accumulate to a greater extent in gastrointestinal tissues than in other tissues, or in the blood, of normal or tumor-bearing rats [2,39,41]. OXO limits the gastrointestinal toxicities of FT by competitively inhibiting OPRT and thus inhibiting the phosphorylation of 5-FU to FUMP within the gastrointestinal tract [2,28,30,39,40]. Furthermore, OXO decreases the formation of 5-FdUMP via 5-FUMP in gastrointestinal tissue, thereby indirectly protecting the activity of TS, leading to a reduction in gastrointestinal toxicity [2,24,28,29,42].

Preclinical studies with S-1

In animal studies, S-1 achieved prolonged concentrations of 5-FU in the blood and tumors, allowing for effective and sustained antitumor activity [2,34,37,43–46]. In the preclinical studies, S-1 showed antitumor activity in experimental models of rodent tumors and human xenografts [2,31,37,44–48]. In rats with Yoshida sarcoma, and in nude rats and mice implanted with human colon, stomach, head and neck, and breast cancer cell lines, S-1 significantly inhibited tumor growth [2,37,46]. The antitumor activity observed in various rat tumors and human xenografts, was better than other oral fluoropyrimidines [37,43,46]. In the nude rat system, three tumors, stomach (H-81), colon (KM12C) and breast (H-31), showed marked regression with S-1, but not with UFT (tegafur/uracil) [37,46]. Activity was also observed with S-1 in pancreatic and lung cancers, when transplanted s.c. to rodents [46]. The results of these preclinical studies suggested that oral S-1 would be active against various human cancers. Additionally, Cao *et al.* observed, in rats bearing advanced colorectal cancer, a 4- to 6-fold TS inhibition with S-1 and 5-FU; however, S-1 was superior to 24-h infusion of 5-FU in suppressing free TS [48]. S-1 also showed significant antimetastatic effect in the mouse Lewis lung carcinoma and L5178Y metastasis models, and inhibited the growth of tumors in nude rats in which human gastric and colorectal cancer cell lines were orthotopically implanted [2,37,44,46]. Recently, Mori *et al.* demonstrated that the therapeutic activity of S-1 was significantly greater than that of 5-FU in the prevention of peritoneal metastasis of human gastric cancer cells in nude mice [49].

The preclinical studies also confirmed a low gastrointestinal toxicity with S-1, due to the protection afforded by OXO [2,31,37,40]. The optimal molar ratio of the three components in S-1 was defined using tumor-bearing rats [28,34]. In Cynomolgus monkeys, diarrhea developed with consecutive administration of FT + CDHP; however, with the addition of OXO the diarrhea was inhibited. Similarly, in Beagle dogs, diarrhea developed with consecutive administration of FT + CDHP, but was also inhibited with the addition of OXO [50]. In the consecutive administration of FT + CDHP in Beagle dogs, stomatitis occurred [40,50]. However, with the addition of OXO, the development of stomatitis was either prevented or decreased [40,50]. The co-administration of CDHP with 5-FU also appears to suppress the 5-FU-augmented convulsions in mice suggesting a decreased risk of development of neurotoxicity [40]. Yoshisue *et al.* also noted that repeated simultaneous administration of OXO and FT in rats protected the activity of TS in gastrointestinal mucosa [by decreasing FdUMP via FUMP from 5-FU (Fig. 3)], and could result in reduced gastrointestinal toxicity [42].

In pregnant rats and rabbits, S-1 produced fetal visceral and skeletal abnormalities, and retarded ossification [51]. Thus, with the observation of teratogenicity in animal studies, it is recommended that S-1 should not be administered to patients who are or may be pregnant. Furthermore, in rat studies, excretion of S-1 components in milk has also been reported [51]. Therefore, breast feeding should be discontinued in nursing mothers receiving S-1.

When S-1 was administered alone or in combination with cisplatin (CDDP) in nude rats, S-1 produced significant inhibition of tumor growth [inhibition rate (IR) = 89%] versus control ($p < 0.05$); the S-1 + CDDP combination produced a marked inhibition of tumor growth (IR = 99%) which was significantly greater than CDDP alone ($p < 0.05$) [52]. In human gastric cancer xenografted in nude mice, S-1 (day 1–21) CDDP (day 1) showed better results than S-1 alone [53]. More recently, Araki *et al.* demonstrated the potentiated antitumor effect in Yoshida sarcoma-bearing rats when S-1 was combined with CDDP [2,54]. These studies suggested that the combination of S-1 and CDDP may be promising for further evaluation in clinical trials.

As the preclinical studies suggest that S-1 was at least as effective as 5-FU and other oral fluoropyrimidines, with relatively mild toxicity, clinical trials commenced with the phase I program.

Clinical studies with S-1: phase I and PK

An initial phase I study with S-1 was conducted in Japan, with once- and twice-daily administrations of the compound [55]. For the once-daily administration, PK and safety were evaluated with dose escalations of 25–200 mg/body as a single dose and for 28 consecutive days [28,29,55]. The twice-daily administration was conducted at doses of 50–100 mg/body for 28 consecutive days. The maximum allowable dose for the once-daily administration was from 150 to 200 mg/body/day, or for the twice-daily administration from 75 to 100 mg/body/

administration [28,29,55]. The dose-limiting factor in both schedules was myelosuppression, mainly leukopenia [28,29,55]. Other adverse reactions were rash and vomiting. Diarrhea and stomatitis were mild (grade 1), except those observed at a dose of 200 mg/body/day [55]. Most adverse reactions resolved within 14 days of discontinuation. In the PK study, after single S-1 administration, the plasma concentrations of 5-FU increased in a dose-dependent manner and were maintained at a high level for 12 h [28]. The maximum plasma concentration of 5-FU was attained at approximately 4 h after administration of S-1 at any dose, with a $t_{1/2}$ of approximately 2–3 h. However, 12 h after administration of S-1 a high concentration was still observed. Based on these results, the recommended dose for the early phase II study was 75 mg/body twice daily for 28 consecutive days, followed by a 14-day rest [28,29,55].

To further investigate the PK of S-1, Hirata *et al.* administered 80 mg/m^2/day in two divided doses for 28 consecutive days in 12 patients with advanced cancers [29]. The PK analysis was conducted on 12 patients for single administration and on 10 patients for consecutive administration. The average single dose per body surface area was 35.9 mg/m^2 (31.7–39.7 mg/m^2). Plasma 5-FU PK parameters were as follows: peak plasma concentration (C_{max}), 128.5 ± 41.5 ng/ml; t_{max}, 3.5 ± 1.7 h; area under the curve $(AUC)_{0-14}$, 723.9 ± 272.7 ng·h/ml; and $t_{1/2}$, 1.9 ± 0.4 h. There were no fluctuations in PK in the 28-day consecutive regimen nor was there any drug accumulation. The investigators concluded that the PK of orally administered S-1 was almost similar to that of continuous i.v. infusion of 5-FU [29].

In the US, Hoff *et al.* investigated the clinical pharmacology of S-1 at dose levels of 30–40 mg/m^2, comprising of two daily doses [56,57]. A course consisted of 28 consecutive treatment days, followed by a 1-week rest. Sixteen patients were enrolled; all were evaluable for toxicity and 15 patients for response. At 30 mg/m^2, two of nine patients developed grade 3 hyperbilirubinemia or diarrhea [56,57]. At 40 mg/m^2, dose-limiting diarrhea occurred in three of the three patients. Thus, the protocol was amended to include a dose level of 35 mg/m^2 and grade 3 or 4 diarrhea or hyperbilirubinemia was observed in three of four patients at this dose level [56,57]. The dose of 30 mg/m^2 was thus considered as the maximum tolerated dose (MTD). The PK of S-1 was characterized by rapid absorption and was consistent with first-order kinetics. A durable partial response was observed in a patient with colorectal cancer. Based on the results from this study, the investigators recommended a dose of 30 mg/m^2 twice daily for future studies, where diarrhea could be expected as the most frequent adverse event [56,57].

In the Netherlands, a phase I trial was conducted using doses of 25–45 mg/m^2 twice daily for 28 consecutive days followed by a 1-week rest in patients with advanced solid tumors [58]. At the dose level of 25 mg/m^2, the toxicities were mild and the dose level was elevated to 45 mg/m^2. However, at 45 mg/m^2, grade 3 and grade 4 diarrhea was observed in one and two patients, respectively. The dose of 45 mg/m^2 was defined as the MTD in chemotherapy naive or minimally chemotherapy exposed patients, with diarrhea being the dose-limiting toxicity (DLT). Thus the dose was decreased to 35 mg/m^2. No severe adverse events were observed at 35 mg/m^2 and the dose was then increased to 40 mg/m^2, where grade 3 or 4 diarrhea was observed in two out of three patients who had received extensive prior chemotherapy and in two out of eight patients who had not received extensive prior chemotherapy. Two responses were observed in patients with recurrent gastric and primary gastric/esophagus carcinomas. The investigators recommended a dose of 40 mg/m^2 twice daily for patients who had not received extensive prior chemotherapy and a dose of 35 mg/m^2 for patients who had received extensive pre-treatment [58].

A phase I trial with a once daily administration of S-1 for 21 consecutive days, followed by a 1-week rest, was conducted in the US in 18 patients with refractory malignancies [59,60]. Of 16 evaluable patients, six were treated at a dose of 50 mg/m^2/day and 10 were treated at 60 mg/m^2/day. At the 50 mg/m^2/day level, DLTs were observed in one of six evaluable patients and at the 60 mg/m^2/day level, DLTs were observed in four of 10 evaluable patients. The DLTs included diarrhea, nausea/vomiting, fatigue and hyperbilirubinemia. The MTD in this study was 50 mg/m^2/day and the investigators recommended a phase II dose of 50 mg/m^2/day of S-1 once daily for 21 consecutive days [60]. The PK findings showed a prolonged $t_{1/2}$ and 5-FU AUC at least 10-fold higher than reported in previous studies of equitoxic doses of tegafur/uracil [60]. Pharmacodynamic analysis demonstrated a correlation between diarrhea grade and 5-FU C_{max} and 5-FU AUC.

Yamada *et al.* compared the PK of a continuous i.v. infusion of 5-FU to S-1 [61]. Ten patients with gastric cancer received a continuous i.v. infusion of 5-FU (250 mg/m^2/day) for 5 days, followed by a washout period of 9 days and then received oral S-1 (40 mg/m^2/twice daily) for 28 consecutive days. Plasma concentrations of 5-FU and FBAL were measured on day 1–5 of both treatments. The C_{max} and AUC of plasma 5-FU for S-1 was significantly higher than that of the continuous i.v. infusion 5-FU (mean 5-FU C_{max}: 230 versus 93 ng/ml; mean 5-FU AUC_{0-10ht}: 1364 versus 728 ng·h/ml, for S-1 versus continuous i.v. infusion of 5-FU, respectively). In terms of the production of plasma FBAL, through the degradation process of DPD, the C_{max} and AUC was higher with

continuous i.v. infusion 5-FU compared to oral S-1 (mean FBAL C_{max}: 1157 versus 198 ng/ml; mean FBAL AUC_{0-10ht}: 9465 versus 1725 ng·h/ml). This lower FBAL concentration observed with S-1 further demonstrates the inhibitory effects of the CDHP component of S-1 on DPD, which might result in a lower incidence of neurotoxicity and cardiotoxicity.

Ikeda *et al.* evaluated the PK of S-1 in animal models and in patients with impaired renal function [62]. Fifty percent of CDHP is excreted in the urine, thus the investigators postulated that renal dysfunction might directly affect the DPD inhibition and cause increased 5-FU concentrations. In rabbits with impaired renal function, plasma concentrations of FT, 5-FU, CDHP and OXO were determined after S-1 injection. The PK was also analyzed in four patients with unresectable gastric cancer, with various degrees of renal impairment, receiving single and consecutive doses of S-1. In both settings, higher and longer 5-FU concentrations and subsequent increases in AUC were observed, most likely due to the retention of CDHP. Thus the investigators suggested individualized dosing of S-1 and PK monitoring in patients with impaired renal function [62].

In Japan, the DLT of S-1 is myelosuppression, whilst in Western countries it is diarrhea [2,55–61]. Although the differences remain unexplained, a possible reason might be that FT is converted more slowly to 5-FU in Asians than in other ethnic groups [2,9,56,58,63].

Clinical studies with S-1: phase II and III

A number of clinical studies with single-agent S-1 were conducted in patients with gastric cancer in Japan. A summary of these trials is presented in Table 1 [2,64–76]

S-1 phase II trials: gastric cancer

In one early phase II trial and two pivotal late phase II trials, overall RRs of 53.6%. (15/28) [64,65] and 44.6% (45/101) [66–68] were obtained. In an early phase II study, S-1 was initially administered at 75 mg/body twice daily for 28 days, followed by a 14-day washout period. The main adverse events in these initial studies were hematological. The early phase II trial, which dosed up to 75 mg b.i.d. S-1, observed grade 3 or higher: leukopenia (10.7%), neutropenia (17.9%), thrombocytopenia (7.1%), diarrhea (7.1%) and anorexia (10.7%) [64,65]. By the additional analysis, it was shown that the rate of discontinuation of administration due to these adverse reactions was markedly lower in patients given S-1 at 90 mg/m^2 or less. Therefore, 80 mg/m^2/day (40 mg/m^2/b.i.d.) for 28 consecutive days, followed by 14 days rest, was set as the standard treatment schedule of late phase II studies in the consideration of safety profile (Table 2). The two pivotal late phase II Japanese trials dosed up to 60 mg b.i.d. S-1 and observed fewer grade 3 or higher adverse events, i.e. leukopenia (2%), anemia (5%), diarrhea (1%) and malaise (1%) [66–68]. In the combined analysis of these studies, the median survival time (MST), 1-year survival rate and 2-year survival rate were 244 days, 37% and 17%, respectively.

Other trials of S-1: gastric cancer

Miyamoto *et al.* studied the relationship between immunoreactivity to TS and DPD in biopsy specimens and the effects of S-1 in 41 advanced gastric cancer patients (Table 1) [69]. In this study, there was no significant difference between RR and median survival time between TS-positive and TS-negative patients nor between DPD-positive and DPD-negative patients. The investigators concluded that S-1 was effective in the treatment gastric cancer patients, regardless of intratumoral TS and DPD immunoreactivity status; however, they suggested that studies with larger numbers should be conducted to confirm these results.

Yoshida *et al.* observed a RR of 47.4% in patients receiving 75 mg/m^2/day (37.5 mg/m^2/b.i.d.) S-1 (Table 1) [70]. In this study the principal adverse events were grade 3 bone marrow suppression in three patients, severe diarrhea (one patient), liver dysfunction (one patient), and a few cases of nausea and vomiting. Yoshida *et al.* concluded that S-1 was effective for advanced and recurrent gastric carcinomas, especially peritoneal disease.

Similarly, Inaba *et al.* found 40 mg/m^2/b.i.d. S-1 to be a promising regimen for gastric cancer with peritoneal dissemination, with 1- and 2-year survival rates of 63.2 and 23.7%, respectively, and eight patients (44.4%) survived for 1 year or more (Table 1) [71]. Grade 3–4 adverse reactions consisted of reduction in hemoglobin level (three patients) and hyperbilirubinemia (one patient).

A comparative study of 40 mg/m^2/b.i.d. S-1 versus a control group (consisting of fluoropyrimidine-based chemotherapy) in gastric cancer patients with peritoneal dissemination, showed a significantly better median survival with S-1 ($p = 0.0008$) (Table 1) [72]. Furthermore, grade 3–4 adverse reactions caused by S-1 occurred in only one patient.

More recently, three phase II Japanese trials have shown that S-1, at doses of 40 mg/m^2/b.i.d., is effective in the treatment of both CT-naive gastric cancer patients and patients who have received prior CT (Table 1) [73–75]. RRs of 44–47.6% were observed in CT-naive patients and 12.5–35% in patients who had received prior CT for gastric cancer. As expected, the RR decreased as the resistance/failure to number of prior chemotherapies increased. Nevertheless, S-1 offers promising activity in previously treated gastric cancer patients.

Table 1 Clinical trials with single-agent S-1 in gastric cancer [2,64–77]

Study	Prior CT	S-1 dose (mg/m^2)	No. of patients (evaluable)	CR (*n*)	PR (*n*)	RR (%)	MDR (days)	MST (days)	Main side-effects
Early phase II trial in Japan									
Horikoshi *et al.* [64,65] 1996, 1999	+	50, 75 b.i.d. × 4 wk[a]	28 (25)	0	15	53.6	84	298*41.4%	leukopenia, anemia, diarrhea
	–								
Late/pivotal phase II trials in Japan									
Koizumi *et al.* [66,67] 2000, 1998	–	40 b.i.d. × 4 wk	50 (49)	0	20	40.0	135	207*36%	hemoglobinemia, leukopenia, neutropenia, diarrhea
Sakata *et al.* [68] 1998	–	40 b.i.d. × 4 wk	51(49)	1	24	49.0	68	250*37%	hemoglobinemia, granulocytopenia, leukopenia, diarrhea, malaise
Other trials in Japan									
Miyamoto *et al.* [69] 2000	NA	40 b.i.d. × 4 wk	41				NA	253	NA
			TS+: 24	13		TS+: 54		TS+: 284	
			TS–: 17	9		TS–: 53		TS–: 189	
			DPD+: 18	11		DPD+: 61		DPD+: 338	
			DPD–: 23	11		DPD–: 48		DPD–: 207	
Yoshida *et al.* [70] 2001	NA	37.5 b.i.d. × 4 wk	22 (19)	0	9	47.4	NA	NA	bone marrow suppression, diarrhea, nausea vomiting
Inaba *et al.* [71] 2002		40 b.i.d. × 4 wk	NA	NA	NA	NA	NA	437*63.2%	anemia, hyperbilirubinemia
Osugi *et al.* [72] 2002		40 b.i.d. × 4 wk vs control	34	NA	NA	NA	NA	S-1: 257 Control: 118 (p=0.0008)	hyperbilirubinemia
Moriwaki *et al.* [73] 2003	–	NA	45 (44) CT		14	31.8	NA	395*53%	neutropenia, anorexia, nausea, vomiting, diarrhea
	+		naive: 25		11	CT naive: 44			
			prior CT: 19		3	prior CT: 16			
Cho *et al.* [74] 2003	–	40 b.i.d. × 4 wk	69 (58)	2	25	38	NA	336*48%	NA
	+		prior CT: 25			prior CT: 36			
Takahashi *et al.* [75] 2003	–	40 b.i.d. × 4 wk	29	0	11	37.9	NA	426*50.2	leukocytopenia, neutrocytopenia
	+		CT naive: 21	0	10	CT naive: 47.6			
			prior CT: 8	0	1	Prior CT: 12.5			
Kimura *et al.* [76] 2003	–/+	40 b.i.d.	27				NA	NA	incidence ADR:
		4W/2W	4W/2W: 14	0	3	21.4			4W/2W: 93%
		2W/1W	2W/1W: 13	0	3	23.1			2W/1W: 77%
Phase II trial in Europe									
Chollet *et al.* [77] 2003	–	40, 35 b.i.d. × 4 wk	7 (3) 23 (19)	NA	NA	31.6	223	NA	non-hematological toxicities led to the reduction of the dose from 40 to 35 mg/m^2/b.i.d.

TS+ = thymidylate synthase positive; TS– = thymidylate synthase negative; DPD = dihydropyrimidine dehydrogenase; DPD+ = dihydropyrimidine dehydrogenase positive; DPD– = dihydropyrimidine dehydrogenase negative; NA = not available. 4W/2W: S-1 administered for 4-week periods with a 2-week interval between sessions. 2W/1W: S-1 administered for 2-week periods separated by 1-week drug-free intervals. ADR = adverse drug reaction.
[a]mg/body.
*1-year survival rate (%).

Table 2 The standard recommended dose of S-1 (40 mg/m^2/b.i.d.) in Japan is determined by the body surface area of the patient

Body surface area (m^2)	Initial dose level (mg/dose)[a]
<1.25	40
1.25–1.5	50
>1.5	60

[a]The initial dose can be increased one dose level, with an upper limit of 75 mg. The initial dose can also be decreased with a lower limit of 40 mg [51].

In an attempt to further reduce the incidence of adverse events, Kimura *et al.* compared a new S-1 schedule (where the drug is administered for 2-week periods separated by 1-week drug-free intervals [2W/1W]) to the standard schedule (4-week dosing regimen with a 2-week interval between sessions [4W/2W]) (Table 1) [76]. In the 2W/1W group, the overall incidence of adverse reactions tended to be lower than in the 4W/2W group (77 versus 93%, respectively). Grade 3 adverse events were observed in only two of the 13 patients in the 2W/1W group (anorexia, fatigue) and in four of the 14 patients in the 4W/2W group (hemoglobinemia, anorexia, fatigue, skin lesion). No grade 4 events were observed in either group. The percentage of patients who were on study at 6 months was 85% in the 2W/1W group and 40% in the 4W/2W group. The RR between the two groups was similar. The results from this study suggest that the 2-week regimen may offer an additional alternative to the 4-week schedule, and possibly lessen adverse reactions and prolong the medication period [76].

In the first European trial with single-agent S-1 for the treatment of gastric cancer, S-1 was administered orally twice daily at 40, then 35 mg/m^2/b.i.d. for 28 days every 5 weeks (Table 1) [77]. The initial dose of 40 mg/m^2/b.i.d. was reduced to 35 mg/m^2/b.i.d., due to the occurrence of significant non-hematological adverse events at the higher dose. At 35 mg/m^2/b.i.d., a RR of 26.1% [95% confidence interval (CI) 12.0–45.1%] was observed in 23 enrolled patients and 31.6% (CI 14.7–53.0%) in 19 evaluable patients. At 35 mg/m^2/b.i.d., the median duration of response (six patients) was 223 days (range 108–828 days) and of stable disease was 111 days (range 68–411 days). We concluded from this study that 35 mg/m^2/b.i.d. oral S-1 for 28 days every 5 weeks is effective and has an acceptable safety profile in European CT-naive gastric cancer patients, with a RR similar to other fluoropyrimidines.

In the majority of these phase II trials, S-1 achieved RRs around 40%, which was at least as good, if not better than, the efficacy observed with other active chemotherapies for the treatment of gastric cancer [64–70,74,75]. Furthermore, S-1 exhibited a favorable safety profile [64–77].

Based on the early and late pivotal phase II Japanese trials, S-1 was registered for the treatment of gastric cancer in Japan and went on the market in 1999. It was therefore logical to continue the development of S-1 in the treatment of gastric cancer with confirmatory phase III studies, combination trials and investigate its use as a neo-adjuvant treatment. These trials will be discussed in further detail, following the discussion on S-1's activity in colorectal cancer and other tumors.

S-1 phase II trials: colorectal cancer (CRC)

Three pivotal Japanese studies were conducted with single-agent S-1 for the treatment of CRC, which included one early phase II trial and two late phase II trials (Table 3) [64,65,78–80].

In the early phase II trial, the RR was 16.7%; however, in patients who had received no prior CT, the RR was 25.0%. Furthermore, stable disease was observed in 43.3% of the patients [64,65]. The overall median survival was 358 days, with a 1-year survival of 49.4%.

Ohtsu *et al.* and Sawada *et al.* conducted two late/pivotal phase II trials in Japan (Table 3) [78–80]. In these studies, S-1 achieved similar RR to those of infusional 5-FU + leucovorin (LV), with manageable toxicity [79]. In the first study, the RR in 43 colon cancer patients was 34.9% and 36.8% in 19 rectal cancer patients. Incidence of grade 3–4 toxicity included: leukopenia (4.8%), neutropenia (12.9%), anemia (6.5%), thrombocytopenia (8.1%), diarrhea (1.6%), anorexia (4.8%), nausea/vomiting (1.6%) and malaise (1.6%). There were no treatment related deaths and none of the 53 patients treated as out patients required hospitalization due to adverse events [79]. In the second study, a high RR (39.5%) was maintained, with a lower incidence of grade 3–4 toxicity, i.e. neutropenia (5.3%), hyperbilirubinemia (7.9%) and diarrhea (2.6%) [80].

In the European study performed by the EORTC Early Clinical Studies Group, advanced/metastatic CT-naive CRC patients were treated with S-1 at a dose of 40 mg/m^2/b.i.d. for 28 consecutive days, repeated every 5 weeks; however, the dose was reduced during the study to 35 mg/m^2/b.i.d. because of a higher than expected number of severe adverse drug reactions (Table 3) [81]. Twenty-four percent (nine patients) of the 37 evaluable patients had a partial response and 46% (17 patients) had stable disease, with 30% (11 patients) experiencing progressive disease. Diarrhea was the most frequent adverse event. We concluded that S-1 is an active agent for the treatment of CRC, and recommended further investigations to establish the optimal dose and schedule of S-1 [81].

These trials showed that S-1 has similar, and in some cases superior activity, to other active chemotherapies for the treatment of CRC patients, with a promising safety profile. However, caution should be applied with indirect

Table 3 Phase II trials with single-agent S-1 in colorectal cancer [64,65,78–81]

Study	Prior CT	S-1 dose (mg/m^2)	No. of patients (evaluable)	CR (*n*)	PR (*n*)	RR (%)	MDR (days)	MST (days)	Main side-effects
Early phase II trial in Japan Horikoshi *et al.* [64,65] 1996, 1999	+	50, 75 b.i.d. × 4 wk[a]	30	0	5	16.7	120	358	leukopenia, anemia, diarrhea, stomatitis
	–								
Late/pivotal phase II trials in Japan Ohtsu *et al.* [78,79] 1998, 2000	–	40 b.i.d. × 4 wk	62	0	22	35.5	171	365	neutropenia, thrombocytopenia, anemia, leukopenia, anorexia
Sawada *et al.* [80] 2002	– adjuvant CT permissible > 6 months prior	40 b.i.d. × 4 wk	38	0	15	39.5	NA	NA	neutropenia, hyperbilirubinemia, diarrhea
Phase II trial in Europe Van den Brande *et al.* [81] 2003	–	40, 35 b.i.d. × 4 wk	47 (37)	0	9	24.3	NA	NA	diarrhea

[a]mg/body.

literature comparisons with phase II trials and confirmatory phase III trials are warranted [65]. The manufacturing approval of S-1 for CRC was applied for in Japan in 2002.

S-1 phase II trials: other solid tumors

An overview of the phase II trials with single-agent S-1 in the treatment of other solid tumors [including head and neck cancer, breast cancer, non-small cell lung cancer (NSCLC), and pancreatic cancer] is shown in Table 4(a and b).

One early phase II trial and one late phase II trial were conducted in Japan to evaluate the efficacy and safety of single-agent S-1 in the treatment of head and neck cancers (Table 4a) [82–85]. These studies demonstrated that S-1 was an active agent for the treatment of advanced or recurrent head and neck cancer (RRs ranged from 28.8 to 46.2%), with manageable adverse events. S-1 has recently obtained registration approval in Japan for the head and neck indication.

Two phase II Japanese trials also demonstrated that S-1 was an effective agent for the treatment of advanced or recurrent breast cancer, with response rates of 40.7 and 42% (Table 4a) [86–88]. Thus, S-1 offers promising activity for the treatment of breast cancer, and further evaluations of this compound both as a single agent and in combination are warranted.

Table 4(b) provides a summary of the activity S-1 in the treatment of NSCLC and pancreatic cancer. Two phase II studies with single-agent S-1 for the treatment of advanced NSCLC (stage IIIB/IV) produced RRs of 12.5–22% [89,90]. In the early phase II trial, unresectable stage IIIB or IV patients were entered onto the trial and two or less prior CT schedules for their disease was permissible [89]. The median overall age was 68 years. The RR for the entire study population was 12.5% (Table 4b), and in terms of clinical stage it was 8.3% for stage IIIB and 14.3% for stage IV [89]. The projected median survival was 8.4 months (27.3% 1-year survival) for 56 eligible patients and 9.5 months (26.7% 1-year survival) for previously untreated patients [89]. The initial dose in the early phase II study was 75 mg/body/b.i.d., but after four out of the six patients had grade 1–2 skin eruption, this was reduced to 50 mg/body/b.i.d. [89]. The incidences of grade 3 or more severe adverse events were: anemia (5.4%), leukopenia (5.4%), neutropenia (5.4%), thrombocytopenia (1.8%), anorexia (3.6%), diarrhea (3.6%) and general fatigue (5.4%) [89]. Furuse *et al.* concluded that S-1 showed modest activity in the treatment of pretreated NSCLC patients, and suggested that a late phase II study for advanced disease and a phase II study of S-1 in combination with CDDP should be undertaken [89]. Kawahara *et al.* conducted the late phase II trial and evaluated S-1 at a dose 40 mg/m^2/b.i.d.

Table 4a Phase II trials with single-agent S-1 in other solid tumors [30,82–88]

Study	prior CT	S-1 dose (mg/m^2)	No. of patients (evaluable)	CR (*n*)	PR (*n*)	RR (%)	MDR (days)	MST (days)	Main side-effects
Head and neck cancer									
Early phase II									
Inuyama *et al.* [82,83] 1998	NA	50, 75 b.i.d. × 4 wk[a]	26	1	11	46.2	NA	NA	hemoglobinemia, leukopenia, neutropenia, stomatitis, anorexia
Late phase II									
Inuyama *et al.* [84,85] 2001	+	40 b.i.d. × 4 wk	59	4	13	28.8		344	anemia, leukopenia, neutropenia, stomatitis, anorexia
	–		CT naive: 6 prior CT: 45			CT naive: 33.3 prior CT: 26.7			
Breast cancer									
Early phase II									
Taguchi *et al.* [86,87] 1996, 1998	+	50, 75 b.i.d. × 4 wk[a]	27 (25)	4	7	40.7	298.3	782	hemoglobinemia, leukopenia, neutropenia, anemia, anorexia, nausea, vomiting, fatigue
Late phase II									
Sano *et al.* [88] 2000	–/+	40 b.i.d. × 4 wk	81 (83)	6	28	42.0		910	neutropenia, anorexia, nausea, vomiting, fatigue, diarrhea, stomatitis

[a]mg/body.

Table 4b Phase II trials with S-1 in other solid tumors [30,89–94]

Study	prior CT	S-1 dose (mg/m^2)	No. of patients (evaluable)	CR (*n*)	PR (*n*)	RR (%)	MDR (days)	MST (days)	Main side-effects
NSCLC cancer									
Early phase II									
Furuse *et al.* [89] 2001	–	50, 75 b.i.d. × 4 wk[a]	56				149.8	*27.3%	thrombocytopenia, leukopenia, neutropenia, anemia, anorexia, fatigue
	+		CT naive: 40 prior CT: 16	0 0	5 0	12.5			
Late phase II									
Kawahara *et al.* [90] 2001	–	40 b.i.d. × 4 wk	59	0	13	22.0	104.3	312.1 *41.1%	anemia, thrombocytopenia, neutropenia, anorexia, diarrhea, stomatitis, malaise
Combination phase II									
Sakai *et al.* [91] 2003	–	$S\text{-}1_{40\ \text{b.i.d., 3 wk}}$ $CDDP_{60,\ \text{d 8}\times\text{4–5 wk}}$	56 (55)	1	25	47.3		336.6 *45%	neutropenia, anemia, anorexia, diarrhea, vomiting
Pancreatic cancer									
Okada *et al.* [92] 2002	–	40 b.i.d. × 4 wk	19	0	4	21.1	NA	167	erythrocytopenia, anorexia, nausea hematotoxicity, anorexia
Hayashi *et al.* [93,94] 2002, 2003	NA	$S\text{-}1_{40\ \text{b.i.d}}$	31	1	6	22.6	NA	463	
		$S\text{-}1_{40\ \text{b.i.d.}}$ + $CDDP_{30,\ \text{d 1+8}}$	37	0	16	43.2		443	

[a]mg/body.
*1-year survival rate (%).

in 59 eligible CT-naive advanced NSCLC patients [90]. The RR was 22.0% (13/59) (95% CI 12.3–34.7%) (Table 4b), with a RR of 22.7% (5/22) in stage IIIB and 21.6% (8/37) in stage IV patients [90]. The duration of response was 3.4 months (1.1–13.7 months or longer), the overall survival time was 10.2 months (95% CI 7.7–14.5 months, 41% 1-year survival rate) [90]. In this study, the grade 3 or 4 toxicities were: hemoglobinemia (1.7%), neutropenia (6.8%), thrombocytopenia (1.7%), anorexia (10.2%), diarrhea (8.5%), stomatitis (1.7%) and malaise (6.8%) [90]. The investigators concluded that S-1 was an active single agent for the treatment of NSCLC and that further studies with S-1 in combination with other active agents was warranted.

Sakai *et al.* carried out a phase II trial with S-1 in combination with CDDP, where S-1 was administered orally at 40 mg/m^2/b.i.d. for 21 consecutive days while CDDP (60 mg/m^2) was administered i.v. on day 8 in CT-naive stage IIIB/IV NSCLC patients (Table 4b) [91]. The RR was 47% (95% CI 34–61%), with a survival time of 11 months and a 1-year survival rate of 45% [91]. In addition to this promising activity, toxicity was manageable and generally mild to moderate, with grade 3 and 4 hematological toxicity included neutropenia (29%) and anemia (22%) [91]. No grade 4 non-hematological toxicity was observed and grade 3 toxicity included anorexia (13%), vomiting (7%) or diarrhea (7%). The authors suggested a randomized trial comparing S-1 + CDDP to control as a first-line treatment for NSCLC [91].

Two phase II trials have been conducted to evaluate the efficacy and safety of S-1 for the treatment of pancreatic cancer (Table 4b) [92–94]. One trial assessed single-agent S-1 at a dose of 40 mg/m^2/b.i.d. for 28 consecutive days, repeated every 6 weeks in CT-naive patients with advanced pancreatic cancer [92]. In this trial, a RR of 21.1% was observed, with 52.6% of patients experiencing stable disease [92]. The main grade 3–4 toxicities were: anemia (21.1%), anorexia (15.8%) and nausea (15.8%). S-1 was found to be active and well tolerated in advanced pancreatic patients; the results will be confirmed in a large phase II trial [92]. Hayashi *et al.* undertook a phase II trial to evaluate the feasibility and efficacy of S-1 as either a single agent or in combination with CDDP for the treatment of patients with locally advanced or recurrent pancreatic cancer. S-1 was administered at a dose of 40 mg/m^2/b.i.d. for 28 days, followed by a 2-week period of no treatment [93,94]. The combination regimen consisted of S-1 b.i.d. for 21 days and CDDP 30 mg/m^2 on day 1 and 8, followed by a 2-week rest. The RR with single-agent S-1 was 22.6% (95% CI 7.8–37.4%, the median survival time was 463 days) and with S-1 + CDDP was 43.2% (95% CI = 27.2–59.2%, survival was 443 days) [93,94]. Two cases of grade 3 anorexia and one grade 3 hematotoxicity were observed among patients treated with S-1 alone, whilst in the S-1 + CDDP group, three grade 3 and two grade 4 hematotoxicity, and three grade 3 anorexia incidences occurred [93,94]. The investigators concluded that S-1 alone and S-1 + CDDP were active with acceptable toxicities for the treatment of pancreatic cancer [93,94].

S-1 phase III overview and post-marketing survey

Based on the efficacy and safety observed in phase II trials with S-1 for the treatment of gastric cancer, phase III trials have been undertaken. A phase III trial of 5-FU alone versus irinotecan + CDDP versus S-1 alone in advanced gastric cancer patients has been initiated by the Japan Clinical Oncology Group, with a planned enrollment of 450 patients (JCOG 9912) [28,95]. The primary endpoint of this study is overall survival, with 5-FU being the control arm of the study. Another ongoing phase III trial is comparing 5-FU + LV to S-1 alone, where 200 patients will be enrolled.

A phase II pilot study was conducted to evaluate S-1 (50–60 mg/body/b.i.d. for 28 consecutive days followed by a 14-day rest) as neo-adjuvant CT for potentially resectable scirrhous gastric cancer [96]. In this pilot study, five patients were enrolled, received two courses of S-1 and then underwent resection. The RR for neo-adjuvant S-1 was 60% (3/5 patients) with the remaining two patients experiencing stable disease. Three of the five patients had curative resection, whilst the other two patients had non-curative resection due to localized peritoneal dissemination [96]. No grade 3 or 4 adverse events were observed with short-term neo-adjuvant S-1. In this pilot study, pre-operative S-1 produced high response rates and the investigators concluded that S-1, as neo-adjuvant CT for scirrhous gastric cancer, should be verified by proper phase II and III trials [96].

The effect of additive S-1 in patients with incompletely resected gastric cancer (peritoneal seeding) has been addressed in a Japanese feasibility study, where seven patients were enrolled [97]. Patients underwent R1 resections by aggressive cytoreductive surgery, thereafter S-1 (40 mg/m^2/b.i.d.) was administered for 28 consecutive days followed by a 14-day rest, repeated every 6 weeks. In three out of the seven patients, S-1 was administered for 1 year, while the treatment was discontinued in four patients due to disease progression. S-1 was found to be feasible as an additive CT for resected gastric cancer with peritoneal seeding [97].

Currently, a phase III study of surgery alone versus surgery followed by S-1 in patients with curative resection of gastric cancer is in progress [28]. In this randomized trial, patients with stage II, IIIa or IIIb disease will receive either surgery alone or surgery and

a 1-year treatment of S-1 as adjuvant treatment [28]. The required sample size for this Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer study is 1000 patients, with overall survival as the primary endpoint.

Based on a phase I/II study in patients with advanced gastric cancer with S-1 in combination with CDDP, where an RR of 76% (19/25 patients) was obtained [98], a phase III trial was planned and is currently ongoing. Three hundred patients with metastatic disease are required, randomizing patients to receive either S-1 alone or S-1 + CDDP.

The results from these phase III trials are awaited.

Following the manufacturing approval of S-1 in 1999 for the treatment of gastric cancer, the Japanese Ministry of Health and Welfare recommended a post-marketing surveillance for 1 year with a target population of 3000 patients. The purpose of the survey was to confirm the safety of the drug in this patient population. S-1 was administered according to the Japanese product labeling (see Table 2) for 28 consecutive days followed by a 14-day rest [28,99]. A total number of 3294 patients were evaluable for safety. Approximately 60% of patients had received prior CT. A total of 3294 courses were administered, with 28% of patients receiving one course, 25% received two courses and 47% received three or more courses [99]. The overall incidence of adverse reactions was 75%, which included 25% grade 3 or higher adverse events. The frequency and severity of grade 3 or higher adverse events from the interim analysis in the post-marketing survey were similar to those of the combined results of the late phase II pivotal studies in gastric cancer [28,66–68,99]. Hematological toxicities were the predominant adverse events and included grade 3 or higher: leukopenia (2.7%), neutropenia (6.2%), anemia (6.3%) and thrombocytopenia (1.6%) [29,99]. Grade 3–4 non-hematological toxicities were: diarrhea (2.0%), anorexia (6.2%), nausea/vomiting (2.1%) and stomatitis (1.4%) [28,99]. Patients with impaired renal function had a significant higher incidence of grade 3 or higher hematological toxicities [99]. This might be explained by the retention of CDHP which was the finding from the PK study by Ikeda *et al.*, where higher and longer-lasting 5-FU concentrations were obtained in experimental renal failure animal models and in patients with impaired renal function [62]. Thus, the post-marketing survey confirmed that: (i) S-1 could be safely administered to patients with gastric cancer, and (ii) patients with impaired renal function needed to be carefully monitored and tailored dosing might be required in this group of patients [28,99]. Kawai *et al.* registered 91 patients from the National Cancer Center Hospital East onto the post-marketing survey [100]. Of these 91 patients, 51 were CT-naive (47 of which were evaluable for efficacy and safety analyses). The median number of S-1 courses was five. Adverse events were generally mild to moderate, with 10% or less of patients experiencing grade 3 or higher toxicities. The RR was 43% (two complete responses and 18 partial responses), the median survival time was 11.1 months and 2-year survival rate was 33%. Once again, this sub-analysis of the post-marketing survey confirmed the safety of S-1 and that the oral drug was highly active with favorable long-term survival in patients with gastric cancer.

Clinical studies with S-1 in combinations: phase I and II in gastric cancer

CDDP, CPT-11 (irinotecan) and docetaxel are active agents for the treatment of gastric cancer. Phase I/II trials have been conducted with S-1 in combination with these agents and the studies are described in further detail below and summarized in Table 5(a and b).

S-1 in combination with CDDP

A preclinical study demonstrated the combination of S-1 (20 mg/kg) and low-dose CDDP (1 mg/kg) significantly inhibited cell growth (IR = 99%) in ovarian cancer-bearing nude rats compared to CDDP alone ($p < 0.05$). [101]. In addition to the induced tumor regression, the S-1 and low-dose CDDP was associated with a low toxicity.

Ohtsu *et al.* conducted a phase I/II trial with S-1 in combination with CDDP in patients with advanced gastric cancer (Table 5a) [98]. The aim of the study was to determine the MTD of CDDP with a fixed dose of S-1. CDDP was administered as a 2-h infusion on day 8 at dose levels of 60–80 mg/m^2 and S-1 was administered orally at a fixed dose of 40 mg/m^2/b.i.d. for 21 consecutive days. This schedule was repeated every 4–5 weeks [28,98]. The MTD was 70 mg/m^2 for CDDP and the recommended dose for further phase II trials was 60 mg/m^2 CDDP as a 2-h i.v. infusion on day 8 + 40 mg/m^2/b.i.d. S-1 for 21 consecutive days [28,98]. The regimen was highly active, with a RR of 76.0% (95% CI 54.9–90.6) and stable disease in a further four patients. The toxicities were generally mild. The PK results suggested no drug interaction between CDDP and S-1 [98].

A low-dose CDDP (biweekly at a dose of 15 mg/m^2 infused for 30 min) was combined with oral S-1 (40 mg/m^2/b.i.d.) in 12 patients with advanced or recurrent gastric cancer (Table 5a) [102]. In this study, the RR was 41.7%, with a survival time of 13.3 months. Grade 3 leukopenia was observed in one case. Thus, the investigators concluded that this CT was effective for patients with advanced or recurrent gastric cancer, and recommended that the possibility of leukopenia should be monitored [102].

Table 5a Phase I/II trials with S-1 in combination with CDDP for the treatment of gastric cancer [8,98,102–107]

Study	CT regimen	CT dose (mg/m^2)	No. of patients (evaluable)	CR (*n*)	PR (*n*)	RR (%)	MDR (days)	MST (days)	Main side-effects
Phase I/II trials									
Ohtsu *et al.* [98] 2001	S-1	40 $_{\text{b.i.d., d 1–21}}$	25	0	19	76.0	126	349	neutropenia, anemia, anorexia, fatigue
	CDDP	60, 70, 80 $_{\text{i.v., d 8}}$ q 4 wk	phase I: 12 phase II: 13						
Kamata *et al.* [102] 2001	S-1	40 $_{\text{b.i.d.}}$	12	NA	NA	41.7	NA	407	leukopenia
	CDDP	15 $_{\text{i.v., biweekly}}$							
Baba *et al.* [103] 2003	S-1	40 $_{\text{b.i.d., d 1–21}}$	12	0	8	66.7	NA	NA	anemia
	CDDP	60 $_{\text{i.v., d 8}}$ q 5 wk							
Tsujitani *et al.* [104] 2003	S-1	40 $_{\text{b.i.d., d 1–28}}$	15	0	8	53.3	122.4	NA	leukopenia
	CDDP	5, 10 $_{\text{i.v., d 1, 3, 5, &/w}}$							
Neo-adjuvant CT									
Saikawa *et al.* [105] 2003	S-1	30 $_{\text{b.i.d. d 1–21}}$	9	NA	NA	55.6[a]	NA	NA	NA
	CDDP	6 $_{\text{i.v., d 1–5, 8–12, 15–19}}$							
Akiba *et al.* [106] 2003	S-1	40 $_{\text{b.i.d., d 1–21}}$	22	NA	NA	50	NA	NA	hematological
	CDDP	5–20 $_{\text{i.v., d 1–5, 8–12, 15–19}}$							
CDDP + CPT-11 with sequential S-1 + CDDP or visa versa: phase II trials									
Tsujitani *et al.* [107] 2002	CDDP	40$_{\text{once a wk}}$	11 (11)		5	45.5 → 50.0[P] (3/6)	NA	NA	neutropenia, thrombocytopenia, diarrhea, anorexia, renal failure
	CPT-11	30$_{\text{once a wk} \times 3\text{ wk}}$							
	S-1	40 $_{\text{b.i.d., d 1–28}}$	17 (15)		8	53.3 → 0[P] (0/5)			
	CDDP	7$_{3 \times \text{a wk}}$							

[a]Five of nine cases showed significant effect with severe fibrosis diagnosed in histology.
[P]In cases with disease progression after the initial treatment, patient received sequentially the alternative treatment.

Table 5b Phase I/II trials with S-1 in combination with CPT-11 or docetaxel for the treatment of gastric cancer [28,108–113]

Study	CT regimen	CT dose (mg/m^2)	No. of patients (evaluable)	CR (*n*)	PR (*n*)	RR (%)	Recommended dose
S-1 + CPT-11: phase I/II trials							
Narahara *et al.* [108] 2002	S-1	40 $_{\text{b.i.d., d 1–21}}$	19 (18)	NA	10	55.6	recommended dose: S-1: 40$_{\text{b.i.d., d 1–21}}$ CPT-11: 80$_{\text{i.v., d 1, 15}}$
	CPT-11	40–120 $_{\text{i.v., d 1, 15}}$ q 4 wk					
Komatsu *et al.* [109] 2002	S-1	40 $_{\text{b.i.d., d 1–14}}$	15	1	7	53.0	recommended dose: S-1: 40$_{\text{b.i.d., d 1–21}}$ CPT-11: 125$_{\text{i.v., d 1, 15}}$
	CPT-11	100–150 $_{\text{i.v., d 1, 15}}$ q 4 wk					
Yamashita *et al.* [110] 2003	S-1	40 $_{\text{b.i.d., d 1–14}}$	16	1	8	56.3	recommended dose: S-1: 40$_{\text{b.i.d., d 1–21}}$ CPT-11: 80$_{\text{i.v., d 1, 8}}$
	CPT-11	70–100 $_{\text{i.v., d 1, 8}}$					
Yamada *et al.* [111] 2003	S-1	40 $_{\text{b.i.d., d 1–14}}$	12 (7)	0	5	71.5	recommended dose: S-1: 40$_{\text{b.i.d., d 1–14}}$ CPT-11: 150$_{\text{i.v., d 1}}$
	CPT-11	100–150 $_{\text{i.v., d 1}}$ q 3 wk					
Komatsu *et al.* [112] 2003	S-1	40 $_{\text{b.i.d., d 1–14}}$	16		NA	54.2	NA
	CPT-11	125 $_{\text{i.v., d 1, 15}}$ q 4 wk					
S-1 + docetaxel: phase I trial							
Yoshida *et al.* [113] 2003	S-1	40 $_{\text{b.i.d., d 1–14}}$	9 (7)		NA	71.4	recommended dose: S-1: 40$_{\text{b.i.d., d 1–14}}$ TXT: 80$_{\text{i.v., d 1}}$
	TXT	40–60 $_{\text{i.v., d 1}}$ q 3 wk					

TXT = docetaxel.

Baba *et al.* treated 12 patients with advanced gastric cancer with S-1 (40 mg/m^2/b.i.d. for 21 days) plus CDDP (60 mg/m^2 on day 8) every 5 weeks (Table 5a) [103]. This combination had a high RR (66.7%), with S-1 antitumor effects being enhanced whilst the toxicity remained mild to moderate (grade 1–2). Four patients had stable disease and there were no patients who had progressive disease. The overall incidence of grade 3–4 adverse events was 16.6%, as two patients experienced grade 3 anemia. The results from this study suggested this combination was feasible at the outpatient clinic (apart from a short stay in hospital during the infusion of CDDP with hydration) [103].

Tsujitani *et al.* evaluated the efficacy and safety of S-1 (40 mg/m^2/b.i.d. for 28 consecutive days, followed by 14 days rest) plus CDDP [5 or 10 mg/m^2 infused 3 times each week (day 1, 3, 5) during S-1 administration on hospitalization, and once each week (day 1) at the outpatient clinic] (Table 5a) [104]. A RR of 53.3% was observed, with four patients having stable disease and three patients progressive disease. The duration of response was 4 months (range 1–10 months) and the average time to progression was 3.3 months. Adverse reactions appeared in 60% (9/15). The incidence of grade 3 leukopenia was 13% (2/15). The remainder of the adverse events were mild to moderate in severity and most patients could be treated at the outpatient clinic [104].

Two neo-adjuvant trials have been performed with S-1 in combination with low dose CDDP (Table 5a) [105,106]. Saikawa *et al.* treated nine patients with highly advanced gastric cancer, five of whom showed significant effect with severe fibrosis [105]. No grade 4 toxicity was observed and the investigators concluded that the combination of S-1 with low dose CDDP was effective in controlling highly advanced gastric cancer [105].

Akiba *et al.* combined S-1 plus low dose CDDP (5–20 mg/m^2/day) (1–3 cycles before surgery) with or without local radiation for stage IV gastric cancer patients pre-operatively [106]. Radiation therapy (2 Gy/day) was combined with CDDP injection (five days a week) in two cases. Sixteen of the 22 patients (72.7%) underwent surgical resection of the primary tumor and histological curative surgery was performed in 12 patients (54.5%). Among these 16 patients, histopathological effects of the neo-adjuvant CT were observed in 11 patients (50% of all 22 patients). Grade 3–4 hematological toxicity occurred in four patients, while the remainder of the adverse events were grade 2 or below. Thus this trial demonstrated the combination of S-1 with low-dose CDDP as a neo-adjuvant regimen achieved a high RR with low toxicity, which could enable longer-term CT administration prior to surgery [106].

Tsujitani *et al.* conducted a phase II trial with sequential CT with low-dose CDDP/S-1 and CDDP/CPT-11 in 17 and 11 advanced gastric cancer patients, respectively (Table 5a) [107]. In the CDDP plus S-1 combination, S-1 was given at 40 mg/m^2/b.i.d. for 28 days followed by 14-day rest and CDDP at a dose of 7 mg/m^2 3 times a week. In the CDDP plus CPT-11 combination, CDDP was administered at a dose of 40 mg/m^2 and CPT-11 at a dose of 30 mg/m^2, once a week. With CDDP/CPT-11, one course consisted of 3-week administration followed by 1-week rest. Overall, toxicities were generally mild and reversible in both treatment groups. Grade 3–4 adverse events included (for the CDDP/S-1 and CDDP/CPT-11 groups, respectively): anorexia (2/17 and 2/11), diarrhea (0/17 and 1/11), renal failure (1/17 and 0/11), neutropenia (2/17 and 2/11) and thrombocytopenia (1/17 and 1/11). The RRs were 53.3% (8/15) in the CDDP/S-1 and 45.5% (5/11) in the CDDP/CPT-11 groups. Following disease progression after the initial treatment regimen, CDDP/CPT-11 and low-dose CDDP/S-1 were alternatively given to six and five patients, respectively. RRs of these second-line treatments were 50.0% (3/6) in CDDP/CPT-11 and 0% (0/5) in low-dose CDDP/S-1. The investigators concluded that low-dose CDDP/S-1 and CDDP/CPT-11 are effective for advanced gastric cancer with tolerable adverse events. The efficacy of sequential CT with low-dose CDDP/S-1 followed by CDDP/CPT-11 may be better than CDDP/CPT-11 followed by low-dose CDDP/S-1, although the patient numbers with the second-line sequential CT were low and would need further validation.

S-1 in combination with irinotecan

Four phase I trials have evaluated the combination of S-1 with CPT-11 (Table 5b) [108–112]. S-1 was usually administered at a fixed dose of 40 mg/m^2/b.i.d. and the dose of CPT-11 varied.

Narahara *et al.* evaluated a dose of 40 mg/m^2/b.i.d. S-1 (for 21 consecutive days) + 40–100 mg/m^2 CPT-11 (on day 1 and 15), the schedule was repeated every 4 weeks, for the treatment of patients with metastatic gastric cancer (Table 5b) [108]. The MTD was defined at a dose of 40 mg/m^2/b.i.d. S-1 + 100 mg/m^2 CPT-11, the DLT was grade 3 diarrhea and grade 3 rash. The recommended dose for further phase II studies was 40 mg/m^2/b.i.d. S-1 + 80 mg/m^2 CPT-11. The RR was 55.6% and at the recommended dose level a RR of 50.0% was obtained. The PK analysis suggested that there was no drug interaction between S-1 and CPT-11.

Komatsu *et al.* enrolled patients with advanced gastric cancer with S-1 (40 mg/m^2/b.i.d., according to body surface area), administered orally from day 1 to 14, and with three dose escalations of CPT-11 (100–150 mg/m^2), administered on day 1 and day 15, repeated every

4 weeks (Table 5b) [109]. MTD was not reached. Grade 4 neutropenia occurred in one patient at a dose level of 100 mg/m^2 CPT-11 and in two patients at a dose level of 125 mg/m^2 CPT-11; no other grade 4 hematological toxicities were observed. No grade 3–4 non-hematological toxicities were observed, except for one grade 3 nausea/vomiting at the dose level of 100 mg/m^2 CPT-11. From this study, the recommended dose for further phase II studies was 40–60 mg/m^2/b.i.d. S-1 plus 125 mg/m^2 CPT-11. A RR of 53% was obtained. Once again, the PK analysis suggested that there was no drug interaction between S-1 and CPT-11.

Yamashita *et al.* administered S-1 at 40 mg/m^2/b.i.d. (on 14 consecutive days with a 14-day rest period) plus CPT-11 at 70–100 mg/m^2 (on day 1 and 8) (Table 5b) [110]. The MTD was reached at a dose of 100 mg/m^2 CPT-11, at this level the schedule was discontinued in two of three patients due to grade 3 leukopenia and grade 3 thrombocytopenia, respectively. The recommended dose for further study was 40 mg/m^2/b.i.d. S-1 plus 80 mg/m^2 CPT-11. The dose of 80 mg/m^2 CPT-11 was chosen, based on the ability to continue the administration of this combination regimen. In this study, the RR was high (56.3%) and the combination was feasible, thus warranting further investigation, and a phase II study has commenced.

A very high RR was obtained in a phase I study conducted by Yamada *et al.*, although this was in a very small patient population (five out of seven patients had partial response) and RR need to be confirmed with a larger number of patients in the phase II setting [111]. In this trial, CPT-11 was administered at doses of 100–150 mg/m^2 on day 1, every 3 weeks and S-1 40 mg/m^2/b.i.d. from day 1 to 14, every 3 weeks. MTD was not reached and no DLTs were observed at any of the levels in each first cycle. Thus the investigator's recommended dose for further phase II trials was CPT-11 150 mg/m^2 plus S-1 40 mg/m^2/b.i.d. as a first-line therapy for gastric cancer. At this dose level, one patient experienced grade 3 diarrhea and two patients refused to receive the subsequent cycles due to persistent grade 1–2 fatigue.

Following their phase I study results, Komatsu *et al.* conducted a phase II study with S-1 and CPT-11 at the recommended dose (i.e. 40 mg/m^2/b.i.d. S-1 from day 1 to 14 plus 125 mg/m^2 CPT-11 on day 1 and day 15, repeated every 4 weeks) (Table 5b) in 16 CT-naive inoperable advanced gastric cancer patients [112]. Grade 4 neutropenia occurred in six patients, but the patients recovered by skipping doses and treatment continued with dose modifications. Manageable non-hematological adverse events included one patient with grade 3 diarrhea and four patients with grade 3 vomiting. A promising RR (54.2%) was obtained. As CPT-11 at a dose of 100 mg/m^2 produced sufficient efficacy in the phase I study and since grade 4 neutropenia occurred in six cases in this phase II study with CPT-11 at a dose of 125 mg/m^2, one more arm of the CPT-11 at a dose of 100 mg/m^2 was added to the protocol and the two-arm study is currently underway.

S-1 in combination with docetaxel

Yoshida *et al.* conducted a phase I/II combination study of S-1 and docetaxel in patients with advanced or recurrent gastric cancer (Table 5b) [113]. In the phase I part of the study S-1 was administered at a dose of 40 mg/m^2/b.i.d. for 14 consecutive days every 3 weeks and docetaxel was given on day 1 at dose levels: 40, 50 or 60 mg/m^2. The MTD was reached at the 50 mg/m^2 docetaxel plus 40 mg/m^2/b.i.d. S-1 dose level, with three out of six patients experiencing DLTs of neutropenia and allergic reactions. The recommended dose for phase II study was 40 mg/m^2/b.i.d. S-1 and 40 mg/m^2 of docetaxel. The RR was 71.4%. In comparison to historical controls, the PK of docetaxel was not altered by administration of S-1. The investigators concluded that the S-1 and docetaxel combination was active with manageable safety, and the phase II trial is now underway.

Discussion

Although the incidence and mortality associated with gastric cancer is decreasing, it remains the second leading cause of cancer death worldwide [114,115]. The incidence of CRC is highest in Australia, New Zealand, North America, Western Europe and in Japan (40 or more cases per 100 000 of the population in males and 25–30 cases per 100 000 in females), whilst in Africa, Central and South America, and South Central Asia the incidence is lower (5–10 per 100 000 of the male population; and even lower in females) [115,116]. In the UK and US, CRC is the second most common cancer for women after breast cancer and for men after prostate or lung cancer [115,117]. Thus breast, lung, gastric cancers and CRC represent a major public health problem. With improved early detection and surgical techniques, the prognosis for these patients has improved [65]. However, distant metastasis or recurrences require effective chemotherapies.

For many years, 5-FU was one of the few agents to show activity against CRC and gastric cancer [2,5,6,118]. Furthermore, 5-FU has a wide range of activity against numerous other solid tumors and has therefore remained an essential part of the treatment strategy over the last decades. Thus a lot of attention has focused on 5-FU as a foundation for developing new agents with improved efficacy, safety and QoL effects [118]. Improvements over bolus 5-FU have been made with the development of prolonged or continuous infusion and by biochemical modulation with LV. Continuous infusion 5-FU offers RR

and toxicity advantages compared to bolus 5-FU; however, the median survival time of the two administration methods is similar and the requirement of infusion pumps, along with increased costs and risks mean that 5-FU i.v. bolus remained the conventional treatment [2,11,12]. LV provides a source of reduced folate intracellularly; this stabilizes the ternary complex they form with TS and FdUMP (Fig. 4), which increases and prolongs the inhibition of TS, thereby increasing the efficacy of the drug [2]. In a meta-analysis of 5-FU and LV (5-FU/LV) with 1381 advanced CRC patients, 5-FU/LV demonstrated significantly improved RR compared to bolus 5-FU (23 versus 11%, respectively); however, survival was similar (11.5 months with 5-FU/LV versus 11 months 5-FU alone) [2,119]. Significant toxicities include diarrhea, mucositis and neutropenia, with approximately 20–30% of these patients requiring hospitalization [120]. With the combination of 5-FU and LV it seems that toxicity to normal tissues is increased, which appears to be more dependent on the 5-FU dose rather than on the LV dose, necessitating a reduction in the dose of 5-FU [4,121]. In addition to the toxicity, the activity of 5-FU is limited by the short $t_{1/2}$ of 5-FU in plasma, due to DPD, and by the resistance to 5-FU of some tumors with overexpression of TS or low reserves of reduced folates [2]. Thus the development of orally active formulation of 5-FU allowed for 5-FU plasma levels to mimic those of 5-FU continuous infusion, whilst promising improved patient convenience and QoL.

Oral fluoropyrimidines were developed that either acted on the catabolic pathway of 5-FU [i.e. DPD inhibitory fluoropyrimidines (DIF) such as UFT or eniluracil/5-FU], or on the anabolic pathway (i.e. non-DIF/prodrugs such as FT, doxifluridine or capecitabine), or on both the catabolic and anabolic pathways (i.e. DIF, other enzyme inhibitors and non-DIF/prodrugs such as S-1, UFT + LV, BOF-A2). A summary of oral fluoropyrimidines in terms of the composition, advantages over bolus 5-FU, and differences in principal toxicities is provided in Table 6.

FT is a prodrug that is activated through two separate metabolic pathways, i.e. by hepatic cytochrome P-450 enzymes and systemic soluble enzymes (Fig. 4) [6,122,123]. The principal toxicities are gastrointestinal (i.e. nausea, vomiting, diarrhea and mucositis) and neurological (i.e. change in mental status, cerebellar ataxia and coma) (Table 6) [6,124]. The latter has limited the use of FT alone [6].

Doxifluridine is an oral fluoropyrimidine prodrug (Fig. 4); however, its main limitation is its gastrointestinal toxicity [which might be due to the liberation of 5-FU in the small intestine, through the action of thymidine phos-

Table 6 A brief overview of the oral fluoropyrimidines [2,5,6,22,120] (adapted from [6])

Drug	Composition		Potential advantages over i.v. 5-FU	Principal toxicities
	Prodrug	Enzyme inhibitor		
Prodrug only				
FT	yes 5-FU prodrug	no	reliable absorption circulating $t_{1/2}$ 5–12 h	GI, CNS
Doxifuridine	yes 5-FU prodrug	no	reliable absorption	GI, neurotoxicty
Capecitabine	yes doxifluridine prodrug	no	reliable absorption tumor selective	GI, HFS
Enzyme inhibitor only				
Eniluracil + 5-FU	No	yes DIF	reliable absorption ↑5-FU $t_{1/2}$ may overcome 5-FU resistance thus ↑ tumor sensitivity	neutropenia, diarrhea
Prodrug and enzyme inhibitors				
S-1	yes FT/5-FU prodrug FT:OXO:CDHP 1:0.4:1	yes × 2 DIF:CDHP and OXO	reliable absorption ↑5-FU $t_{1/2}$ may overcome 5-FU resistance thus ↑ tumor sensitivity ↓GI toxicity	hematological toxicity, diarrhea
UFT	yes FT/5-FU prodrug	yes DIF:uracil	reliable absorption ↑5-FU $t_{1/2}$	GI
UFT/LV	FT:Uracil 1:4 FT/5-FU prodrug	DIF:uracil TS inhib.:LV		
BOF-A2	yes EM-FU/5-FU prodrug EM-FU:CNDP 1:1	yes DIF:CNDP	reliable absorption ↑5-FU $t_{1/2}$ may overcome 5-FU resistance thus ↑ tumor sensitivity	hematological toxicity, GI

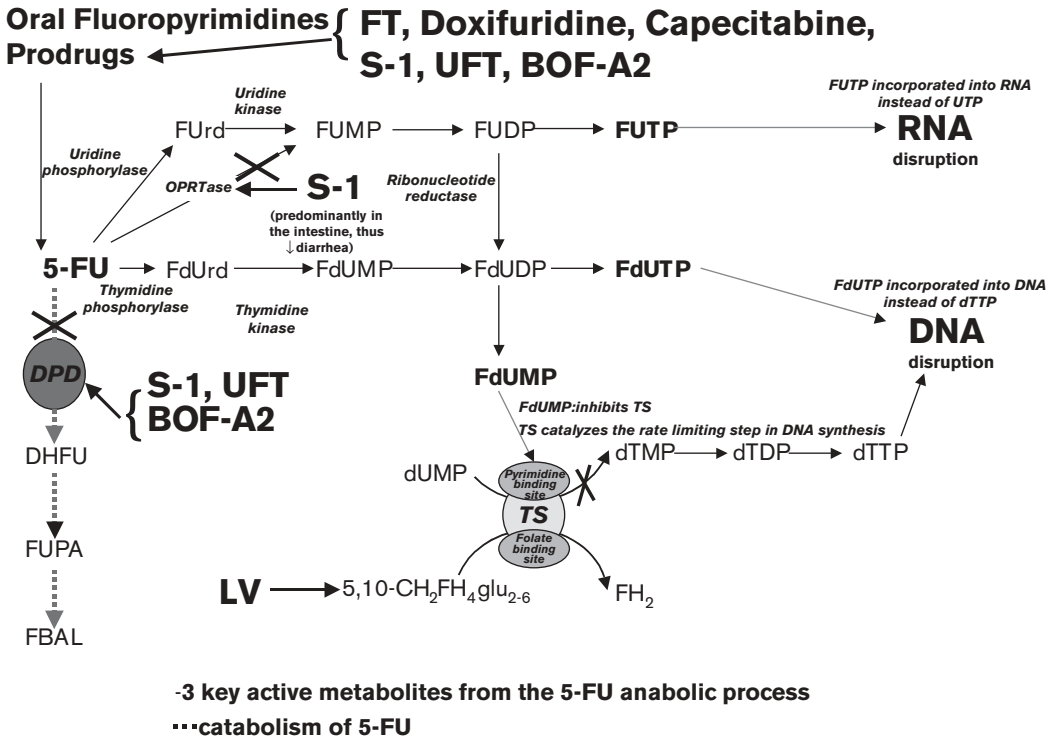
phorylase (TP)] and effects on the CNS (Table 6) [2,120,125,126]. Thus capecitabine was developed as a doxifluridine prodrug, to prevent the metabolism of doxifluridine by TP in the intestine [2].

Capecitabine (Fig. 4) undergoes a three-step activation: (i) in the liver, it is first metabolized to 5′deoxyfluorocytidine (5′-dFCR), by hepatic carboxylesterase; then (ii) 5′-dFCR is deaminated to doxifluridine (5′d5-FUrd) by cytidine deaminase (an enzyme found in liver, plasma, and tumor tissue); then (iii) doxifluridine is then converted to 5-FU by the enzyme TP [2,6]. TP may be more abundant, or have higher activity in tumor than in normal tissue, possibly allowing a higher 5FU concentration in tumor cells with lower exposure to healthy tissues [2,6,127–129]. Capecitabine is active in several solid tumors (Table 6). The main toxicities associated with capecitabine are gastrointestinal (in particular diarrhea, but also nausea, vomiting and stomatitis), hyperbilirubinemia and HFS [2,5,6]. The optimal management of the skin toxicity of the prodrug is still under debate.

Eniluracil (776C85) is a DPD targeted agent (Fig. 4 and Table 6), and was developed in an attempt to enhance the oral absorption and prolong $t_{1/2}$ of 5-FU [6,16]. Preclinical studies showed a 100% oral bioavailability of 5-FU with eniluracil pretreatment and clinical trials showed an oral availability of 5-FU (when administered with eniluracil) of 117 ± 44% [6,120,131–133]. Phase I trials confirmed that the administration of oral 5-FU with oral eniluracil (administered in a ratio of 10:1) can produce 5-FU plasma levels similar to those obtained with protracted infusion 5-FU [120]. The main side-effects are neutropenia, with the 5-day schedule, and diarrhea, with the 28-day schedule [6]. Based on the negative results of some clinical trials in patients with CRC, the further development of eniluracil was discontinued in 2000 [6].

UFT is a mixture of FT and uracil, in a molar ratio of 1:4. Uracil is a natural substrate for DPD and thus competes with 5-FU to bind with DPD, in effect inhibiting the catabolism of 5-FU by DPD (Fig. 4 and Table 6) [2,5,6,120]. Thus a greater concentration of 5-FU is made available for the anabolic pathway, resulting in its anti-tumor activity. Various clinical trials demonstrated that UFT had significant activity in CRC, gastric, breast, and head and neck carcinomas, and many other tumor types [6,120,134]. UFT is now commonly combined with LV. The principal adverse events of UFT/LV are gastrointestinal (diarrhea, nausea, vomiting) [2,5,6,120].

Fig. 4



Mechanism of action of various biochemical modulators and oral fluoropyrimidines [22,24,28–30,31,33]. LV=leucovorin, BOF-A2=emitefur, 5,10-$CH_2FH_4glu_{2-6}$=polyglutamated methylenetetrahydrofolate. Further abbreviations, see Figures 1 and 2. Adapted from [22].

BOF-A2 (emitefur) consist of a prodrug (EM-FU, or 1-ethoxymethyl 5-fluorouracil) and a DIF (CNDP, or 3-cyano-2,6-dihydroxypyridine) in a 1:1 molar ratio (Fig. 4 and Table 6) [6,120,135]. EM-FU is activated predominantly by hepatic enzymes and *in vitro* CNDP was approximately 2000 times more potent than uracil in inhibiting 5-FU degradation [120]. Preclinical studies in Japan showed BOF-A2 prolonged 5-FU $t_{1/2}$ and had potent antitumor activity (with longer survival than 5-FU, or UFT) in murine models and against xenografted human tumors in nude mice [6,120,136–140]. Clinical usefulness of BOF-A2 combined with CDDP was observed for human lung cancers xenografted in nude mice cancer, however the combination was not synergistic [141]. Phase I clinical trials evaluated BOF-A2 administered at 100–800 mg/m^2/once daily or 100–400 mg/m^2/b.i.d. for 28 consecutive days [6,120]. The MTD was 400 mg/m^2 daily for 4 weeks, with DLTs being gastrointestinal (anorexia, diarrhea and stomatitis) and hematological (leukopenia and thrombocytopenia) [6,120,142,143]. In a US phase I/II study, Nemunaitis *et al.* found BOF-A2 at a dose of 200 mg/m^2/b.i.d. for 14 days followed by 7 days of rest to be well tolerated and effective in patients with refractory solid tumors [144]. Efficacy has been observed in phase I/II trials with BOF-A2 in gastric cancer, CRC and NSCLC. The major adverse events with BOF-A2 consisted of gastrointestinal symptoms and myelosuppression [6,144–147]. As with some other oral agents, the further development of emitefur has been halted.

To summarize the main characteristics of S-1, the oral drug combination appears to be as least as effective as, and in many instances have greater activity than, other oral fluoropyrimidines and standard i.v. CTs, particularly in gastric cancer and CRC. Furthermore, the adverse events of S-1 are manageable with principal toxicities similar to the other oral fluoropyrimidines (i.e. myelosuppression and gastrointestinal adverse events). However, HFS was not a problematic toxicity associated with S-1, which is often observed with continuous infusion 5-FU and with capecitabine [65]. Whilst, these indirect literature comparisons should be treated with caution (due to variations in patient populations, prior treatments, differing trial methodologies and definitions, small patient numbers, etc.), oral S-1 demonstrates promising antineoplastic activity. The results from the phase III trials with oral S-1 are awaited to confirm these findings.

Future developments with the oral fluoropyrimidines include: use in combination with other active agents; incorporation in the earlier treatment of solid tumors as part of a multi-modality therapy (i.e. in the neo-adjuvant and adjuvant setting); and integration of various aspects of tumor biology (i.e. TS, DPD activity, etc.) which may predict sensitivity to particular drugs and allow individualization of therapy [148–151]. Whilst it might be considered a disadvantage to combine a standard active i.v. CT with the oral fluoropyrimidines, the 'once-off' administration per cycle of the i.v. CT at an out-patient clinic might not impact too severely on patient convenience. Furthermore, some of these standard active i.v. CTs are undergoing development to produce oral formulations in the not-so-distant future.

In conclusion, we may eventually be moving into the next era of cancer management, with the realization of active oral treatments such as S-1, which provide sustained drug concentrations approximating those of continuous infusion without patient inconvenience, which may lead to equivalent or greater tumor response rates and less toxicity.

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